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SYMPOSIUM ON THE ASSESSMENT
OF MYOCARDIAL FUNCTION

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The Board of *British Journal of Anaesthesia* is prepared to offer a limited number of scholarships (maximum value £2500) for doctors who wish to visit selected centres (maximum three per scholar) in the United Kingdom over a period of not less than 6 weeks. The purpose of the scholarship is for young men and women of outstanding ability in their own country to gain firsthand knowledge of the work of United Kingdom departments and, hopefully, to enable them to establish professional links with contemporaries in the United Kingdom.

It is not intended that visiting scholars would practise anaesthesia within the host department, so that eligibility for United Kingdom registration is not a prerequisite. Applicants should establish through their own head of department that the host departments are willing in principle to receive them. The scholarship is not intended to provide a means for attending courses or conferences or for sitting United Kingdom examinations, although attendance at a 1- or 2-day meeting on a subject relevant to the applicant's stated interest might be considered appropriate.

Applications should be by letter enclosing a curriculum vitae. Applicants should state the centres that they wish to visit, with an indication of the benefit that is likely to accrue to the applicant if the scholarship is granted. Each application should be supported by two references from senior colleagues: the references should be sent separately. Applications for scholarships to be taken up in 1988 should be sent to Professor A. P. Adams, Department of Anaesthetics, Guy's Hospital, London, to reach him no later than May 1, 1988.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

ASSESSMENT OF MYOCARDIAL FUNCTION

The introduction of new drugs and techniques in anaesthesia inevitably leads to questions as to what effects they will have on performance of the heart and circulation. The anaesthetist needs to know specifically if there are likely to be changes which will affect the normal circulation or, with the increasing incidence of coronary artery disease, if there will be deleterious effects if myocardial perfusion is already limited. To answer these questions there are a bewildering variety of techniques of measurement, of animal preparations and clinical investigations. In consequence it becomes difficult for the uninitiated to decide what is going to be significant for clinical practice.

In order to try to help the clinical investigator and the general reader, Professors Van Aken, Lunkenheimer and Merin organized a conference early in 1987 with the specific aim of resolving the merits and limitations of the methods available for assessing myocardial function. Some 27 experts were invited to present reviews of the anatomy, physiology, pathology and biochemistry of myocardial function and of the methods commonly used in such assessments. The Board of the Journal is pleased to be able to publish this issue which summarizes the results of the symposium. In order to be succinct, each author has been asked to concentrate on the essentials of the presentation, to outline what can and what cannot be learnt using the various approaches. We hope that the issue will be an aid to readers when they come to assess the massive data base available for studies of anaesthesia and myocardial function and a guide into developing good clinical practice.

It will become evident from reading the papers that all methods have some limitations. Many reports assume that the myocardial muscle acts as a single entity, but the first paper here shows that such a simple assumption may not be justified in a normal heart, let alone one where there has been

damage from ischaemia. Looking at the myocardium as a pump is a useful perspective but, again, it is important to note the differences between the performance of individual myocardial fibres and the ventricles (or atria) as whole systems.

Animal experiments are important in assessing myocardial effects of drugs. However, each type of experiment using portions of tissues, whole organs in isolation, whole organs *in vivo* with or without the controlling effects of the nervous and endocrine systems, and the additional choice of experiments using anaesthetized animals with or without an open chest or of using conscious animals in which various measurement devices are implanted all pose problems of interpretation of the results. Provided the investigator knows and describes these limitations, then it is possible to use the results to predict what is likely to happen in man. The papers reported here give good guides as to what is possible with techniques that have been in use for some time and with the exciting new developments coming in using, for example, echocardiography. Finally, it is important that studies performed in man are as carefully assessed in terms of the accuracies of the measurements made and the limitations of the investigation as are those in animals. Nevertheless, there is no doubt that the future holds out good prospects for a better prediction of what is likely to happen with new agents, with drug interactions and with the changes likely to be seen with the cardiac pathology seen so commonly with the patients we have to anaesthetize.

The organizers and sponsors of the meeting have provided a useful forum for discussing these issues. We hope this Supplement will give a taste of what can be done and what can be read into the assessment of myocardial function as it is affected by anaesthesia.

J. Norman and M. K. Sykes

THE PROBLEM CREATED BY MYOCARDIAL STRUCTURE IN ASSESSING FUNCTION

P. P. LUNKENHEIMER, K. REDMANN, W. F. WHIMSTER, J. THEISSEN, G. FRIELING AND A. LUNKENHEIMER

In recent years the reassessment of cardiac structure that has taken place has not been adequately correlated with research into myocardial function. Any trial assessing the cardiac effects of the drugs should include an assessment of their effects on the complex force patterns generated within the myocardial meshwork [7].

Although in recent years there have been numerous new agents introduced to support the failing heart, there is still no universally accepted way of quantifying any inotropic action. The problems face not only the cardiologist, but also the anaesthetist who routinely uses drugs with cardiac depressant actions. Anaesthetists may well be in the relatively unfortunate position, in the operating theatre and the intensive care unit, of having to monitor circulatory function without being able to differentiate between effects of the heart on the venous system or on the arterial system.

Furthermore, it is not known what causes ventricular dilatation in myocardial failure, in cardiomyopathy and in myocardial fibrosis. In 1813, Brachet put forward the idea that there were two populations of myocardial fibres [1]. One set was arranged parallel to the surface of the heart and the other arranged radially. He suggested that the parallel fibres would produce ventricular constriction in systole, whereas the radial fibres would actively diminish wall thickness in diastole, producing an active ventricular dilatation. In

consequence myocardial muscle activation would be biphasic. Although no biphasic activation and no radial transmural fibres have been demonstrated, Brachet's concept led to the idea of a dualistic organization for ventricular function [4, 8].

Most clinicians assume that there is a unique myocardial force vector which is exclusively concerned with ventricular emptying. This concept has been supported by Frank [2] and, more recently, by Streeter and Bassett [14]. These authors analysed sections parallel to the surface of what may be an unrepresentative segment of the left ventricle. There is, however, good evidence of an arrangement of myocardial fibres which lie parallel to neither the endocardium nor the epicardium [7, 9].

Among the many dissection studies of the myocardial fibres, the most elaborate is that of Torrent-Guasp [15]. He concluded that myocardial fibres are entwined, as in a rope, with one end at the root of the pulmonary artery and the other at the aortic root. The "rope" is rolled up to form the right and left ventricles. He did not go on to develop an association between this structure and the consequent function of the heart. We believe, from the structure outlined by Torrent-Guasp, that there must be an oblique transmural force vector with a small component acting transmurally. Such a component will oppose systolic wall thickening and must have some bearing on the efficacy of myocardial contraction, especially in sick hearts [7]. In this paper we aim to show that the gaps in our knowledge of myocardial function arise, in part, from ignoring the complex structure of the myocardium.

METHODS

As all methods of examining the heart after its removal from the body introduce some artefact,

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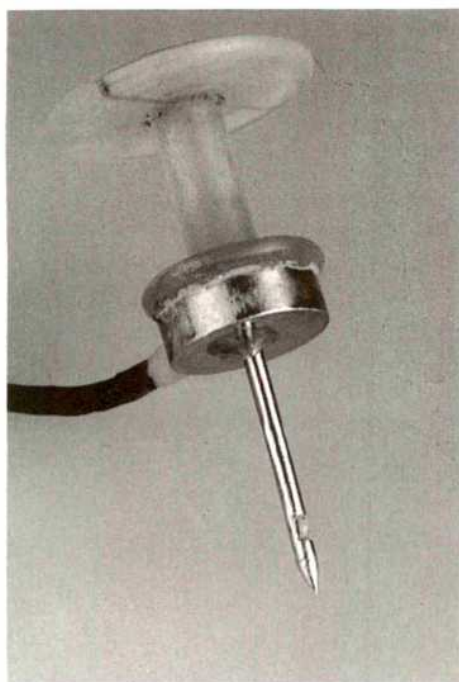


FIG. 1. Needle Force Probe used to measure the mesh tension within the heart muscle. The needle used is inserted through the epicardium in the direction of the endocardium. At any desired depth some fibres of the myocardial network slip into the lateral window. Here they press on a flexible bar which is then deviated from its central position. This deviation is sensed by strain gauges. The type of needle probe shown here has been devised to compare the local mesh tension and the fibre orientation in the different layers of the beating heart.

we have developed a method which enables us to map ventricular forces within the heart with the heart *in situ* and beating normally [6, 8]. We use a needle force probe, 20 mm long and 2 mm thick (fig. 1) with a lateral window near the tip of the probe. The window exposes an inner flexible bar to the adjacent myocardial fibres, enabling the local mesh tension to be measured. The needle is punched into the ventricular wall perpendicular to the epicardium down as far as the endocardium, and is then pulled back in 1.5-mm steps. In each position the probe is rotated around its longitudinal axis until the highest force is measured. In this position we have shown that the myocardial fibres are arranged parallel to the window [8]. Thus the signal provides information about the local mesh tension and the orientation of the local force vector. This in turn is closely related to the orientation of the local fibres.

In any measuring site some six to 12 layers can

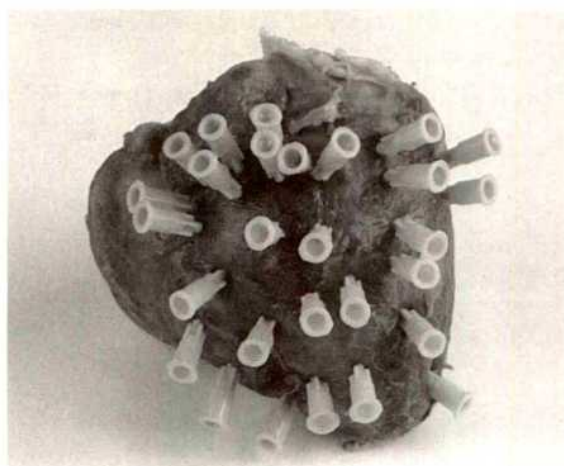


FIG. 2. Dog heart after force mapping in the left ventricular wall in 28 measuring sites, indicated here by hypodermic needles.

be discriminated. In each of five dog hearts some 20 to 30 separate sites have been assessed (fig. 2). In a further three dogs, similar measurements have been made approximately 6 weeks after banding the aortic root to produce a systolic pressure gradient of 20, 30 or 40 mm Hg.

RESULTS

Local force measurements within the ventricular wall showed that there was no unique "surface parallel" arrangement of the myocardial fibres. The relative distribution of the fibres was indicated by the force signals. Ninety percent of signals showed a distinct reduction during the ejection period and in only 10% did we find an afterloaded type of signal in which the force continued to increase during ventricular emptying. In these latter areas we found the measuring window coupled to fibres which did not run parallel to either the endo- or the epicardial surface [8].

In the normal dog the highest mean level of local force was greatest in areas with a high incidence of oblique transmural fibres (fig. 3). These areas are in the basal portions of the ventricles. The highest incidence of twisted fibre bands is to be found in the ventricular bases and in the septum. This finding agrees with those of Torrent-Guasp [15]. In the middle portion of the left ventricular wall, which contributes most to ventricular ejection, the mean local force was lowest.

	Base		Middle		Apex	
	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.
Epi.	50.8 ± 2.9	21.6 ± 1.7	37.3 ± 2.0	15.5 ± 1.2	36.5 ± 2.1	14.7 ± 1.2
Mid.	41.3 ± 2.4	16.2 ± 1.6	26.6 ± 1.1	7.0 ± 0.5	25.1 ± 1.6	8.1 ± 0.8
Endo.	50.2 ± 2.6	19.4 ± 1.7	34.7 ± 1.6	11.2 ± 1.3	28.3 ± 2.2	8.7 ± 1.1

Untrained

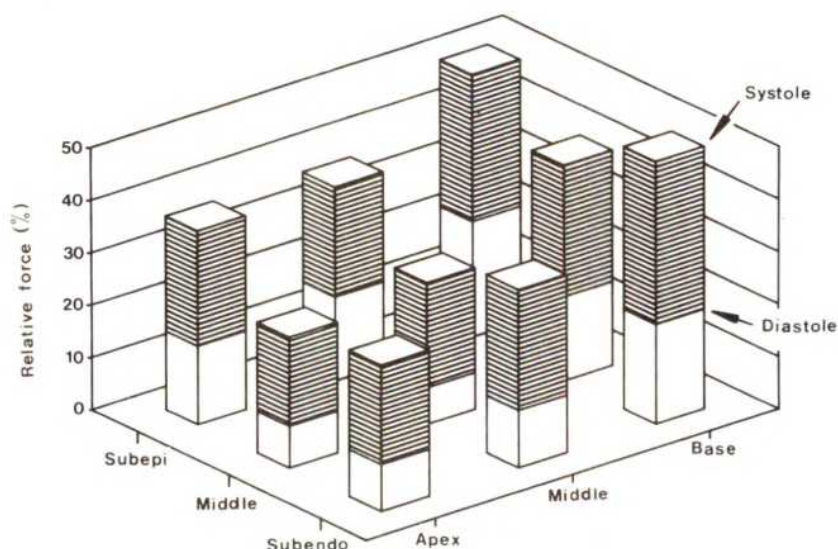


FIG. 3. Mean systolic and diastolic force level in the subepicardium, middle layer and subendocardium of the basal, the middle and the apical portion of the left ventricle. The data from five normal (untrained) dog hearts were statistically processed as follows: the highest force values measured in systole and in diastole, respectively, in all layers at each measuring site were taken as 100%. The data thus normalized were compared for statistical significance between the summed outer (subepi) middle and inner (subendo) layers and between the summed measuring sites in the basal, middle and apical portion, respectively, using Student's *t* test. The local force levels in the longitudinal and in the transmural direction were significantly different. (Mean values ± SEM.)

Torrent-Guasp suggests that this is the most flattened-out and least interwoven part of the fibre net. Thus, the higher the transmural netting and hence the higher transmural force vector, the higher will be the mean level of local mesh tension.

In the dogs subjected to aortic banding, the force levels were highest in the mid zones and at the apex (fig. 4). The forces in the basal areas were likely to be reduced in comparison with forces in the rest of the myocardium.

DISCUSSION

We believe that the functional anatomy of the left ventricle may be described as follows. The

ventricular base and the septum contain a significant proportion of oblique, transmural components. These vary between individuals and with chronic loading conditions. The resultant transmural force vector acts in the direction opposite to that leading to ventricular ejection. It must represent a form of internal work for the ventricle which will depend on the thickness of the wall and thus on the size and state of ventricular training [7]. This transmural force acts as a second source of pre- and afterload. Thus ventricular structure is organized for two functions which, therefore, cannot be measured by conventional haemodynamic measurements. They can be separated when intramyocardial force measurements are made.

	Base		Middle		Apex	
	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.
Epi	48.8±2.7	22.4±2.3	50.7±2.4	23.3±1.6	53.0±6.7	21.8±5.1
Mid.	38.7±1.9	13.1±1.3	42.4±2.3	15.1±1.3	37.5±4.6	13.1±2.5
Endo	45.4±1.6	14.2±1.2	47.8±2.3	15.7±1.3	41.4±3.7	13.2±2.0

Aortic banding

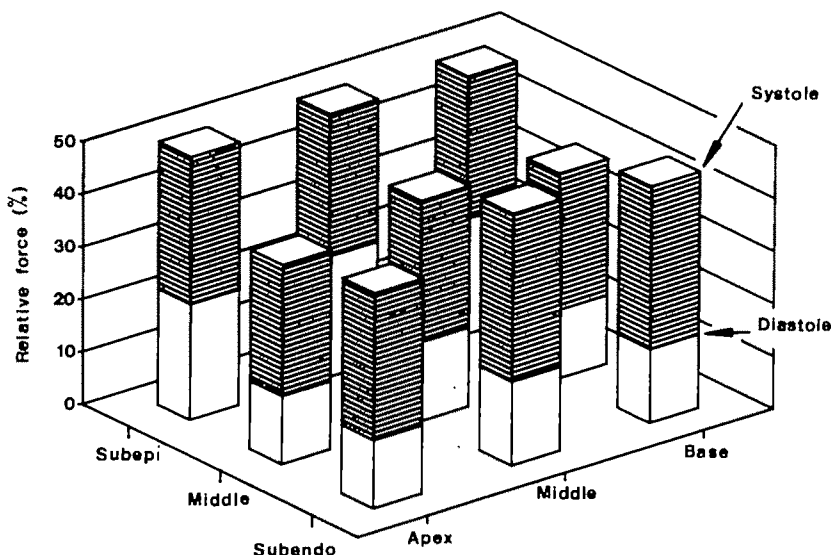


FIG. 4. Local force mapping in the left ventricle of three dogs 6 weeks after aortic banding. The transmural differences in mesh tension still persist. However, the typical force gradient between the basal and middle compartment of the free wall is abolished. (Mean values $\pm$ SEM.)

On the basis of these observations we make two predictions. First, the ventricular septum as well as the basal perivalvular fibres are arranged so as to stabilize the shape of the ventricles rather than be involved in ventricular ejection. The stability of the septum may prevent the ventricles hindering each other during contraction and that of the perivalvular structures may contribute to valvular competence.

Second, by sensing separately the tension in the surface parallel fibres and in the oblique transmural fibres, the afferent nervous system should be able to monitor both ventricular pressure (tangential tension) and size (the transmural force vector). Thus ventricular function could be monitored in terms of the Frank-Starling mechanism, that is in terms of the instantaneous pressure-volume relationship. Intracavitary pressure related to ventricular size could govern adreno-

sympathetic activity when ventricular function reaches the limit of the Frank-Starling mechanisms.

However, this dualistic organization of the myocardial structure complicates any diagnostic access to the heart muscle. Ordinary haemodynamic data do not reflect the pattern of the intramyocardial forces. Wall stress figures calculated from ventricular dimensions and intracavitary pressure are based on unacceptable simplifications of the boundary conditions, especially those concerning ventricular structure [12]. Myocardial force generation can only be measured directly under experimental conditions and, in humans, during cardiac surgery [10, 11]. We see no non-invasive way of assessing the complex pattern of intramural force vectors.

In earlier measurements using Hall-effect sensors we have quantified what can be derived from

ventriculography [5, 7]. This shows that the myocardial mass in the basal portions shortens less than any other part of the ventricular cone, although the force generated is higher in the base than elsewhere. In the base, myocardial fibre contraction is more of an isometric type than in the middle portion, where shortening brings about ventricular emptying. In the basal portion, internal work is obviously greater than that devoted to the haemodynamic (external) performance.

This difference between the two compartments holds true as least for the normal (untrained) left ventricle, although it can be virtually abolished in dogs after a 6-week period of aortic banding. We were able to show earlier [5] that surgical correction of an aortic stenosis does not decrease the magnitude of intramyocardial forces within the early postoperative period. Myocardial hypertrophy is likely to induce a structurally-based increase in internal work. The morphological basis is that there is an increase in the population of fibres not parallel to the surface which will take time to regress. Thus the internal pre- and afterload increase, as do the early systolic rates of increase in force ($+dF/dt$ max) and the later systolic decrease ($-dF/dt$ max). Both these changes will not be reflected adequately by changes in left ventricular pressure (dP/dr max), but they may well be monitored by measuring transients in the wall thickness.

Internal work is dependent on haemodynamic pre- and afterload. In those segments of the myocardium where the internal work is an important component, the contractile state changes with inotropic interventions rather than with filling pressure and aortic impedance. By comparing two compartments, one with an important component of internal work and one which is more loaded by the haemodynamic performance, there is a possibility of separating the direct cardiac effects from the peripheral effects of inotropic drugs which also act on the peripheral vasculature.

We suggest that future investigations should compare the contractile state in the perivalvular ventricular myocardium with that of the mid-point of the ventricle. Transoesophageal echocardiography may give access to the time-dependent variables in ventricular wall dimensions with both segments [3, 13, 16]. One merit of this method is that it can be used during anaesthesia, thereby opening up a new field of intraoperative

monitoring. It may enable the anaesthetist to quantify the negative inotropic effects of anaesthetics and to monitor any inotropic therapy.

SUMMARY

The clinical understanding of the dynamics of myocardial contraction is hampered by an oversimplified interpretation of the intramural pattern of force generation. This limits the anaesthetist's knowledge of the direct effects of commonly used anaesthetics. A discrimination between a negative inotropic effect and changes in pre- and afterload is usually impossible in clinical conditions. By using needle force probes, it is now possible to measure intramyocardial mesh tension in volumes as small as 3 mm^3 . Force mapping in 20 to 30 layers of the hearts of five normal dogs has shown that there are different patterns in the basal, middle and apical portions of the free wall of the left ventricle. An inhomogeneity is also observed when myocardial hypertrophy is produced by a 6-week period of aortic banding. However, this decreased the gradient in wall tension between the basal and the other portions of the ventricle.

Inhomogeneities in wall tension increase the difficulty of assessing the contractile state of heart muscle. It may, however, be useful to compare local wall dynamics in the more isometrically-contracting basal segment with those in the middle portion which brings about most of the emptying of the ventricle. In the future, transoesophageal echocardiography may be used to measure variations in wall thickness which change the global loading conditions in the basal mid-wall compartments of the left ventricle.

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PRINCIPLES UNDERLYING THE ASSESSMENT OF VENTRICULAR AND MYOCARDIAL WORK AND POWER CAPACITY

R. JACOB, M. BRÄNDLE AND G. KISSLING

In differing physiological, pathophysiological and pharmacological conditions the shape and amplitude of any representation of the mechanical state of the heart show considerable variations. In view of the many possible changes in respect of the strength and duration of contraction, it is illusory to think that a single parameter can be used to describe and quantify the state of the heart. This applies to any index, from the concept of the maximum rate of shortening of an unloaded muscle ($v_{\max}$) [13], the various indices of contractility derived during the isometric or isovolumic contraction phases [10] and to the end-systolic pressure-volume relationships [8, 11, 12].

Nevertheless there is still a need for a global quantitative assessment of the mechanical function at the ventricular and myocardial level. In engineering terms, the performance of a pump is expressed as either work or power and, in a broader perspective, in terms of energy turnover and efficiency. Assessment of cardiac function should be made using these parameters, taking into account the physiological basis of muscle contraction. In previous papers we have defined the capacities of the heart for both work and power in terms of the potential work or power available under defined mechanical conditions such as at given pre- or afterloads [2, 4]. It is possible to take into account all the essential factors affecting work by considering the areas in the pressure-volume or in the stress-length diagram. The areas of concern are those between the diastolic and systolic curves [7]. However, an

assessment of the power capacity requires considerations of changes with time as well.

In this paper we aim to show how, in animal investigations, it is possible to evaluate cardiac mechanical performance on the basis of physical and physiological principles, using relatively simple methods. The methods can be applied even if the geometry of the heart is changed markedly. The same principles should be used in assessing those parameters used clinically, such as ejection fractions.

PRINCIPLES OF MUSCLE PHYSIOLOGY

An analysis of the contractile properties of *isolated* muscle can be made on the basis of the relationships between the length of the muscle and its tension and between the tension of the muscle and the rates of changes in length. Additional information can be gained by relating the maximum rate of tension development during contraction and the tension during diastole.

An evaluation of the heart *in situ* also needs to consider the basic properties of muscle, although a number of the arguments can be made only by analogy. For example, the distensibility of the ventricular wall depends not only on the elastic and viscous properties of the myocardium, but also on factors such as the arrangement of the myocardial fibres, the intracoronary vessel pressure and volume, and the influence of the adjacent heart cavities. Similarly, systolic parameters are influenced by coronary perfusion pressure and by the spread of excitation which may be markedly changed by focal lesions.

Figure 1 shows the length-tension relationships of isolated rat ventricular muscle based on studies by Gülch [1]. Figure 1A shows the relationship between length (expressed as a fraction of the maximum length) and tension. The curves des-

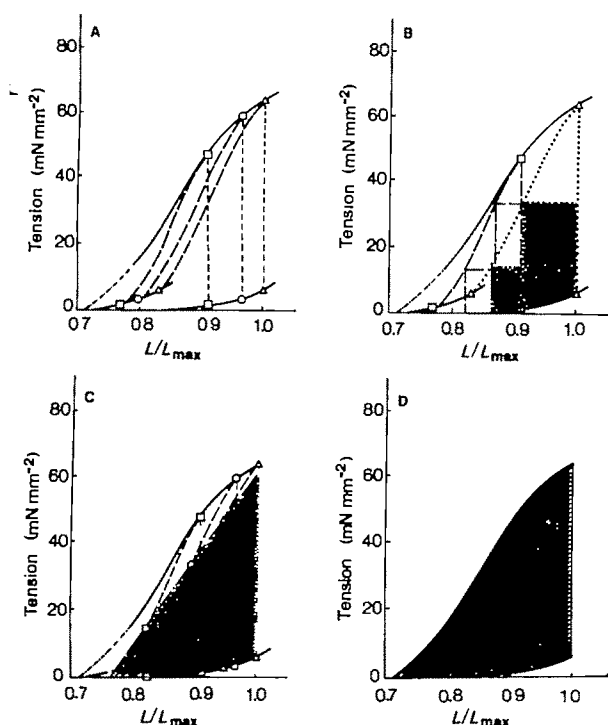


FIG. 1. Length (L)-tension relationships of isolated rat ventricular muscle [1] as a basis for assessing working capacity. A: Resting tension curve (diastole), the curve for isometric tension development and three curves showing the maximum tensions developed with afterloaded contractions. B: Four simplified length-tension loops starting from two differing preload points with two differing afterloads. C: The area between the resting and the "end-systolic" length-tension curves. D: The area between the resting curve and the curve of maximum tension generated from an isometric contraction.

cribing the tension developed from an isometric contraction differ from those where the contraction is afterloaded (as occurs in normal ventricular contraction). These latter curves show variations depending on the initial end-diastolic state. Figure 1B shows the loops relating length and tension for four hypothetical afterloaded contractions beginning at two different preloads and with two afterloads. Starting from a given preload, the length-tension loops extend up to the corresponding maximum curve for the afterloaded contraction. All possible length-tension loops for a given state of "contractility" fall within the area between the resting tension curve and curve of total tension (up to a defined preload) (fig. 1D). This area thus becomes a suitable base for evaluating work capacity. Because normal contraction involves an afterload and some shortening, this area overestimates the actual work

capacity (compare the areas in figure 1D and 1C). The end-systolic length-tension curve (fig. 1C) corresponds to the concept proposed by Sagawa [11, 12]. This curve joins the various end-systolic values produced by varying the afterload.

The pressure-volume (P - V) area has the dimensions of work (Nm) and the analogous length-stress (1 - σ) area has the dimensions of work per unit cross-sectional area (Nm mm⁻²). In analogy to the isolated muscle, the latter parameter is related to muscle length (or ventricular midwall circumference); the resultant "normalized" area (Nm mm⁻² cm⁻¹) gives an index of myocardial working capacity that can be used to compare individuals, including those with hypertrophied and dilated ventricles.

In contrast with an assessment of the slope of the end-systolic pressure-volume or length-stress relationship, the use of the area has a further advantage in that it can also be used when changes in working capacity are brought about by changes in diastolic distensibility which may be seen with contractures, with rigor and with fibrosis [3, 5, 6].

The estimates of power capacity use measurements involving time. Whilst it might appear logical to divide the area P - V or 1 - σ by the duration of systole, this is not acceptable because the duration of systole is itself influenced by the mechanical factors. Thus the maximum rate of pressure increase (dP/dt_{max}) or maximum rate of stress development ($d\sigma/dt_{max}$) is used as an indication of power capacity.

In animal experiments it is possible, by producing a graduated aortic constriction, to vary ejection fraction and shortening velocity so as to produce a representative stress-velocity curve. This has to be done at a high level of ventricular filling since isometric force, and thus the intersection of the curve with the stress axis, will depend on the sarcomere length of the muscle. Whilst extrapolation always presents problems, the area below the curves relating stress and shortening velocity is, in principle, a measure of myocardial power capacity. In any case it is preferable to estimates of the maximum rate of shortening (v_{max}). The maximum instantaneous power is given by the greatest possible area under a stress-velocity curve (see fig. 4B). Finally, the relationship between the maximum rate of stress development ($d\sigma/dt_{max}$) with diastolic stress (σ_D) also is an indication of the myocardial power capacity (see fig. 4A).

EXPERIMENTAL METHODS

Pressure-volume relationships

We have investigated rats anaesthetized with urethane. Some animals were normal Wistar rats and some were spontaneously hypertensive (SHR group). After the chest and the pericardium were opened, a flow probe was placed around the aortic root, and left ventricular pressure measured via a cannula introduced via the apex. Aortic pressure was measured via a cannula inserted through the right common carotid artery. End-diastolic pressure-volume relationships were calculated at the end of each experiment using methods we have previously described [9]. The end-diastolic volume for each beat could then be estimated. The filling pressure was varied either by infusing blood or by occluding the inferior vena cava. The maximal pressure points were produced for roughly isovolumic beats by clamping the descending aorta intermittently.

Sagawa [11, 12] proposed that there is a linear relationship between the end-systolic pressure and volume. In our experience, the isovolumic $P-V$ curve is S-shaped. An extrapolation towards lower end-systolic pressures seems problematic when the curve is flat (fig. 2). With low aortic pressures, without an adequate coronary flow there will be an adverse effect on contractility and thus on $P-V$ and $1-\sigma$ relations [8].

Stress-length and stress-velocity relationships

In order to calculate left ventricular wall circumference and stress we have assumed the ventricle to be a simple sphere. Midwall circumference and wall stress can then be calculated (see reference [8] for details). Extrapolation of a stress-length curve towards the point of zero stress is usually not a problem. Before constructing stress-velocity relationships we have plotted the midwall shortening velocity as a function of time during the entire cardiac cycle. The maximum instantaneous shortening velocity can then be related to the corresponding wall stress.

RESULTS

Drug effects

Figures 2-4 present representative results showing the effects of hexobarbitone $10 \text{ mg kg}^{-1} \text{ min}^{-1}$ in a normal and a spontaneously hypertensive rat. The latter animal was old, which may explain the relatively flat relationship seen with isovolumic

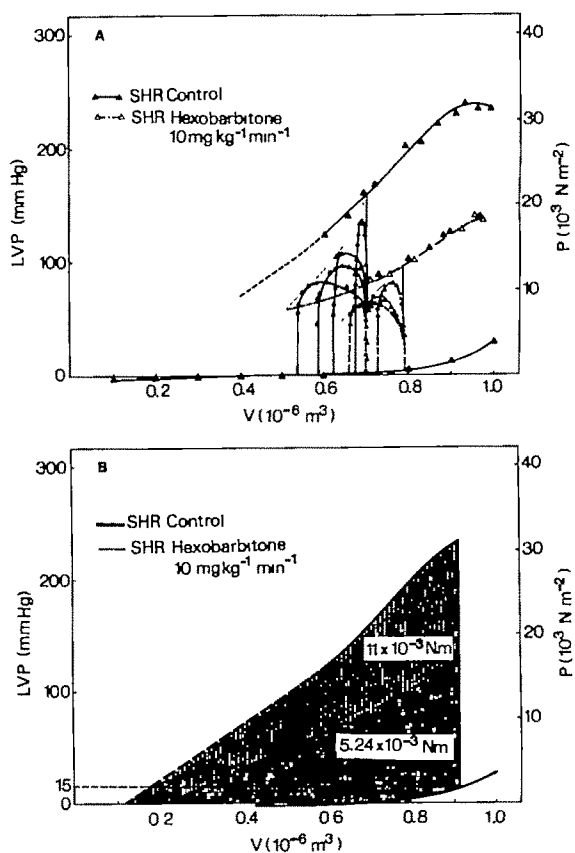


Fig. 2. The left ventricular pressure-volume relationship in an elderly spontaneously hypertensive rat (SHR) under urethane anaesthesia and later under hexobarbitone. A: Isovolumic pressure-volume diagram. The lines join the points obtained under isovolumic conditions and the loops were obtained under conditions of afterloading. B: Left ventricular pressure-volume areas based on conditions with an end-diastolic pressure of 15 mm Hg.

contractions (fig. 2). Figure 2A shows the effects of hexobarbitone on the isovolumic and on the auxotonic pressure-volume relationships. The relationship in diastole is unchanged, but the isovolumic $P-V$ curve is further flattened by the hexobarbitone.

At given end-diastolic volumes both under control anaesthesia and after hexobarbitone, pressure-volume loops were recorded and the aortic pressure was varied by a graduated clamping of the ascending aorta. This gave us the maximum curves for afterloaded contractions which differ from the curve of isovolumic contractions (fig. 2A). The pressure-volume area,

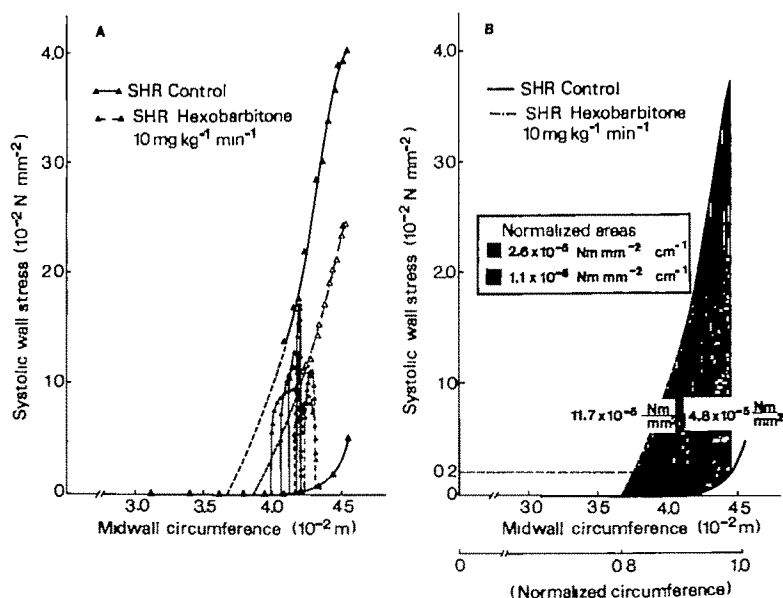


FIG. 3. Left ventricular wall stress-midwall circumference relationships derived from the same experiments as shown in figure 2. A: Isovolumic relationships in diastole and systole with additional stress-length loops obtained with afterloads. B: Stress-length loops obtained with a maximal end-diastolic stress of $0.2 \times 10^{-3} \text{ N mm}^{-2}$. The additional abscissa gives a normalized midwall circumference.

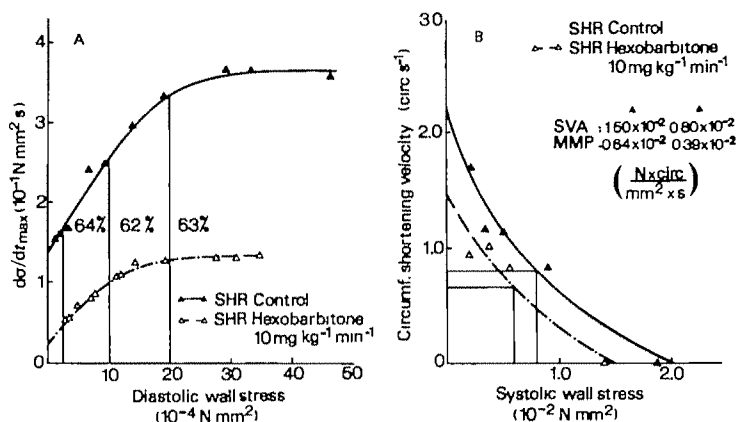


FIG. 4. A: Relationships between the maximum rate of stress development ($d\sigma/dt_{\max}$) and the end-diastolic stress (σ_D). B: Instantaneous circumferential (circumf.) shortening speed as a function of maximal systolic midwall stress. The maximum instantaneous power is given by the largest possible rectangle beneath the stress-velocity curve. The data are drawn from the experiments shown in figure 2 and show, similarly, the depressant effect of hexobarbitone. SVA = Stress velocity area; MMP = maximum momentary power.

after infusing hexobarbitone, is only about 47% of the initial control value (fig. 2B).

In acute experiments it is not necessary to derive stress-length relationships to assess work capacity, but it is necessary when the geometry of the ventricle is changed. The derived relationship

is shown in figure 3. Figure 3A shows isovolumic stress-length curves and some representative stress-length loops. Figure 3B shows the stress-length areas for a given end-diastolic stress, both as absolute values and normalized by relating to a 1-cm muscle length. The percentage reduc-

TABLE I. *Comparison of the effects of hexobarbitone on the various parameters used to assess ventricular and myocardial work and power capacities*

Basis of evaluation	Dimension	Control (193 min ⁻¹)	Hexobarbitone (171 min ⁻¹)	Δ %
Ventricular <i>P-V</i> area	$\times 10^{-3}$ (Nm)	11.00	5.24	53
Normalized $\sigma-l$ area	$\times 10^{-5}$ (Nm mm ⁻² cm ⁻¹)	2.60	1.10	58
$dP/dt_{\max}$	mm Hg s ⁻¹	2005	733	63
$d\sigma/dt_{\max}$ at σ_D 10×10^{-4} N mm ⁻²	$\times 10^{-1}$ (N mm ⁻² s)	2.52	0.97	62
$\sigma-v$ area	$\times 10^{-2}$ (N mm ⁻²)/(circ s ⁻¹)	1.50	0.80	47
(Max. momentary power	$\times 10^{-2}$ (N mm ⁻²)/(circ s ⁻¹)	0.64	0.39	40)

tion produced by hexobarbitone is similar to that seen in the ventricular *P-V* area, as would be expected in acute experiments. The slight numerical difference may be accounted for by the errors of extrapolation and the fact that the pressure-volume and stress-length areas were derived from differing end-diastolic conditions.

The time-dependent variables such as $dP/dt_{\max}$, $d\sigma/dt_{\max}$ (fig. 4A) and stress-velocity relationships (fig. 4B) allow an estimate of the myocardial power capacity and take into account the effects of heart rate. Table I summarizes the effects of hexobarbitone as percentage changes in the various parameters.

Chronic experiments

In the context of assessing the effects of anaesthesia and anaesthetic interventions, the problems involved in evaluating the mechanics of the heart with changes in the geometry and mass of the heart are of lesser interest [3, 7]. Nevertheless, it should be remembered that simple indices such as stroke volume, or even the ventricular *P-V* area, will not be sufficient when the heart is hypertrophied or dilated. Then it is essential to calculate stress-length relationships.

DISCUSSION

The results illustrated here, together with other reports [3, 7], show that in animal investigations a global assessment of left ventricular and myocardial performance is possible using the physical and physiological principles we have described. However, for the intact heart, it must be remembered that we are arguing by analogy with the analyses performed using isolated strips of myocardium. The reasons for this have been mentioned earlier.

The area between the end-diastolic and the isovolumic pressure-volume curve (up to a defined end-diastolic pressure) permits an assessment of the potential ventricular work under various mechanical states, although it renders a slightly overestimated value, for the reason mentioned above. Under clinical conditions, the area between the end-diastolic pressure-volume line and the end-systolic pressure-volume curve (as obtained by Sagawa [11, 12] by varying the filling pressure) can be used as an estimate of working capacity, albeit with some reservations.

The essential feature of our concept is that an assessment of the mechanical properties of the heart should be carried out on the basis of potential work and power. The slope of the end-systolic pressure-volume curve by itself does not take into account the potential effects of changes in the diastolic pressure-volume relationship. Further, even when the end-systolic pressure-volume curve and the working capacity are constant, the time-dependent parameters can change considerably. These differences are more pronounced with drugs such as the catecholamines than with hexobarbitone, and can be particularly marked in chronic experiments.

Finally, it must be remembered that ventricular function will be influenced by the shape and mass of the muscle. In acute studies myocardial function can be assessed by ventricular work or power capacity. Conversion to the stress-length relationship is not needed, but it is worth bearing in mind as part of the basic concept. More empirical parameters such as ejection fraction depend not only on contractility, but also on pre- and afterload, and thus on end-diastolic ventricular pressure and aortic pressure, as well as on ventricular geometry. In acute experiments, potential myocardial work per unit muscle volume

can be derived by relating the pressure-volume loop to the mass of the ventricle. In chronic experiments this does not hold if the geometry is altered because the right-hand limit of the stress-length loop is determined by a definite stress rather than a set end-diastolic pressure. However, the normalized stress-length area (expressed in units of $\text{Nm mm}^{-2} \text{cm}^{-1}$) can be used to compare individual results. Even so, in evaluating ventricular and myocardial power capacities it is also necessary to take into account time-dependent parameters (such as $dP/dt_{\max}$, $d\sigma/dt_{\max}$ or stress-velocity relationships) which involve the effects of heart rate on the velocity of contraction.

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HISTOLOGY OF THE POSTISCHAEMIC MYOCARDIUM AND ITS RELATION TO LEFT VENTRICULAR FUNCTION

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In the cardiac myocyte, as in every highly differentiated cell type, subcellular structure is directly related to the specific function of the cell in the organism. As indicated by Page [8] 47% of the relative volume of a left ventricular myocardial cell is occupied by myofibrils and 36% by mitochondria, the remaining small volume being occupied by sarcoplasmic reticulum, T-system, nucleus etc. Although there is a close correlation between structure and function, when the heart is working within the physiological range, myocardial structure remains quite unaltered. However, when myocardial dysfunction is produced by disease or any other unphysiological condition, myocardial structure will be changed. It is not the aim of this report to provide an overview of all structural abnormalities of the myocardium and their relation to function. What we will do is limit our study to structural myocardial alterations induced by ischaemia and provide evidence that assessment using the electron microscope of ischaemic and postischaemic myocardium can give an insight to the nature of the associated contractile abnormalities. We will also show that examination of myocardial structure is not a useful method for the assessment of postischaemic myocardial dysfunction.

METHOD

Experimental model

Twenty-three mongrel dogs weighing between 18 and 25 kg were premedicated with Hypnorm

0.25 mg kg⁻¹ (fluanisone 10 mg ml⁻¹ and fentanyl 0.2 mg ml⁻¹) i.m. and anaesthetized with sodium pentobarbitone 15 mg kg⁻¹ i.v. After tracheal intubation, the lungs were ventilated with a 50:50 mixture of oxygen and room air using a Bird Mark 7 ventilator. Arterial blood-gases and pH were determined repeatedly throughout the procedure and ventilation was adjusted if necessary to keep these values within the normal range. Additional doses of pentobarbitone were administered as required to maintain anaesthesia. The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. Coronary occlusion was produced by a snare around the left anterior descending coronary artery (LAD) and reperfusion was produced by release of the snare. Coronary occlusion lasted for 90 min and was followed by reperfusion for 2.5 h in one group of animals ($n = 7$) or for 24 h in another group of animals ($n = 6$) and for 1 week in a third group ($n = 10$). In the 24-h and 1-week reperfusion groups the procedure was performed under sterile conditions, the chest was closed after reperfusion and the dogs were allowed to recover. After 24 h the animals were re-anaesthetized and left ventricular function studies were repeated. Finally, the hearts were removed after termination of the procedure in all groups and further processed for histology.

Haemodynamic measurements

General haemodynamics were measured throughout the experiment. These measurements included systolic and diastolic arterial pressure via fluid-filled catheters, left ventricular pressure via a catheter tip manometer, cardiac output via serial measurements using the thermodilution technique, and ECG lead II.

Regional myocardial blood flow was measured using the microsphere technique as described previously [3]. Tracer microsphere injections were made before LAD occlusion, at the end of

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90 min LAD occlusion and after 2.5 h of reperfusion. Global and regional contractility of the left ventricular wall was measured by analysis of end-diastolic and end-systolic contours of a contrast angiogram. These angiograms were performed under control conditions, after 90 min of LAD occlusion and at 2.5 h or 24 h after reperfusion, according to the procedure. Left ventricular volumes were calculated by the area-length method [2, 6]. Correction for heart motion during ejection and identification of nine segments for the study of segmental wall motion were performed according to the method of Leighton [7]. Ejection fraction (%), calculated as end-diastolic volume minus end-systolic volume and divided by end-diastolic volume, was used as a measure of global left ventricular wall motion. As a parameter of segmental wall motion in the LAD area, we calculated the mean percentage shortening of three hemiaxes, which were chosen in such a way that wall motion in the segment of the left ventricular wall spanned by these hemiaxes invariably became abnormal during LAD occlusion.

Histology

The best technique to obtain optimal fixation of the myocardial tissue for electron microscope examination is perfusion fixation of the whole heart. Such a perfusion fixation can be combined with staining techniques for macroscopical delineation of perfusion areas, cell viability and determination of infarct size [3]. In this method, the coronary ostia of the excised heart and the coronary artery at the site of the previous occlusion are cannulated. Both coronary ostia are perfused with a mixture of Ringer solution and Evans blue and, simultaneously, the myocardial tissue which is perfused by the separately cannulated and previously occluded vessel, is perfused with triphenyltetrazolium chloride (TTC), at the same perfusion pressure (50 mm Hg) and at 37 °C. With this technique, the normal myocardium stains dark blue and the "area at risk" or "perfusion area of the LAD" stains brick-red where the tissue is viable and pink-yellow where it is necrotic. The perfusion with these stains is maintained for 10 min and is then switched to a mixture of Evans blue and 2.5% glutaraldehyde for the normal area and to 2.5% glutaraldehyde for the area at risk. When perfusion fixation is used in association with TTC staining as described here, the tissue is inevitably subjected to 10 min of normothermic anoxic perfusion before

fixation. This is a slight drawback, because the first subtle structural abnormalities related to ischaemia and anoxia become apparent, namely, the small osmiophilic granules in the mitochondrial matrix disappear, although the remaining ultrastructure remains unaltered. On the other hand, the advantage of the combination of staining and fixation is that ultrastructural examination can be combined with quantitative assessment of the amount of myocardial necrosis.

After removing the right ventricle, the atria and the valvular structures, the isolated left ventricle was cut in 1-cm thick slices perpendicularly to the long axis. Using calibrated colour pictures of these slices, the left ventricular ring, the perfusion area of the LAD and the infarcted area were reproduced with black ink on a transparent plastic sheet. Total left ventricular area, LAD perfusion area and infarcted area were calculated from data obtained by planimetry performed on the black ink reproductions of the original colour pictures using a Quantimet 900 image analyser. The size of the LAD perfusion bed and the size of the infarcted area were expressed as a percentage of the total left ventricular area.

After colour pictures had been taken for determination of infarct size, small samples of myocardial tissue were removed from the control area, the viable LAD area and the infarcted area. These samples were immersed in a fixative containing 3% glutaraldehyde and potassium oxalate 90 mmol litre⁻¹ adjusted to pH 7.4 with potassium hydroxide 1 mol litre⁻¹. Afterwards these samples were thoroughly washed in the same buffer supplemented with 0.22% sucrose. Postfixation was in 1% osmic acid, buffered to pH 7.4 with veronal acetate 0.05 mol litre⁻¹ containing sucrose 0.093 mol litre⁻¹ for 1 h at 4 °C. After a rinse in the buffer, the samples were dehydrated in graded series of ethanol and routinely embedded in epon. Ultrathin sections were examined in a Philips EM 300 electron microscope after staining with uranyl acetate and lead citrate.

RESULTS

Irreversible myocardial damage: histology and quantification

Electron microscopic analysis of myocardial tissue samples in our experiments was made in a semi-quantitative way. The purpose of this ultra-

TABLE I. Ultrastructural data: control myocardium. + = present; - = absent. Contr. = contracted; relax. = relaxed. Extracell. = extracellular; Intracell. = intracellular. Norm. = normal

Proce- dure No.	Mitochondria				Nuclei		Myofilaments		Oedema		Sarco- lemma	Glycogen	Degree of injury
	Con- fluent cristae	Matrix clearing	Broken cristae	Amor- phous dense bodies	Chro- matin clumping	Pycnosis	Con- traction bands	Contr. or relax.	Extra- cell.	Intra- cell.			
84	-	-	-	-	-	-	-	Relax.	-	-	Normal	+	Normal
85	-	-	-	-	-	-	-	Contr.	-	-	Normal	+	Normal
86	-	-	-	-	-	-	-	Relax.	-	-	Normal	+	Normal
88	Slight	-	-	-	-	-	-	Contr.	-	-	Normal	+	Slight
V-73	-	-	-	-	-	-	-	Contr.	-	-	Normal	+	Normal
V-107	Slight	-	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
V-62	-	-	-	-	-	-	-	Relax.	-	-	Normal	-	Normal
V-104	-	-	-	-	-	-	-	Relax.	-	-	Normal	+	Normal
V-69	-	-	-	-	-	-	-	Relax.	-	+	Normal	+	Normal
V-85	-	-	-	-	-	-	-	Relax.	-	-	Normal	-	Normal

structural study was two-fold: to validate the triphenyltetrazolium staining technique as a reliable method for distinguishing viable from infarcted myocardium; and to assess possible correlations between structural changes induced by ischaemia and postischaemic myocardial function.

Tissue samples from viable and infarcted portions of the LAD area (as indicated by TTC staining), and samples from the control circumflex area, were processed. At least three ultrathin sections were analysed per experiment. These sections were systematically scanned for mitochondrial, nuclear and myofibrillar changes, for the integrity of the cell membrane and for the presence of intra- or extracellular oedema, or both. The results are listed separately for control myocardium, infarcted myocardium and viable myocardium in tables I, II and III, respectively.

The normal appearance of the control circumflex myocardium (table I) testifies to the appropriate processing of the tissue samples. A typical picture is shown in figure 1. In eight of 10 dogs from which control myocardium was analysed, the ultrastructure was completely normal. In the remaining two animals, only minimal signs of tissue injury could be detected.

Ischaemic myocardial tissue is, by definition, irreversibly damaged when cellular integrity is not restored upon reperfusion but followed by necrosis and disintegration. The early diagnosis of irreversibility can only be made by electron microscopic examination because at that stage light microscopy does not show specific lesions.

Definite characteristics of irreversibility can be found at the subcellular level: the mitochondria contain dark, amorphous dense bodies which are most probably precipitations of lipid material and calcium; the sarcolemma is partially disrupted; the nuclear chromatin is abnormally distributed and shows clumping and margination; some degree of intracellular oedema is present; the contractile system itself is usually intact. Upon reperfusion, these typical lesions become even more pronounced. Because of most severe disturbances in membrane function, and even disruption, cell volume regulation is dramatically disturbed and explosive cell swelling occurs upon reperfusion. This is associated with a pathological calcium overload which is responsible for an irreversible accumulation of calcium in the mitochondria. The number of amorphous dense bodies in the mitochondria increases further.

TABLE II. Ultrastructural data: TTC-unstained (infarcted) myocardium. + = present; - = absent. Matrix clearing: + + + = moderate; + + + = severe. Amorphous dense bodies: + + + = numerous; + + + = abundant

Proce- dure No.	Mitochondria			Nuclei		Myofilaments		Oedema		Sarco- lemma	Glycogen	Degree of injury	
	Con- fluent cristae	Matrix clearing	Broken cristae	Amor- phous dense bodies	Chro- matin clump- ing	Pycnosis	Con- traction bands	Contr. or relax.	Oedema				
									Extra- cell.				Intra- cell.
81	Slight	++	-	++		+	+	Contr.	+	+	Rupture	-	Irrev.
83	Slight	++	+	+++		+	+	Contr.	-	-	Rupture	-	Irrev.
85	Slight	++	+	+++		+	+	Contr.	+	+	Rupture	-	Irrev.
13	-	++	+	+++	Prominent	-	-		+	+	Rupture	-	Irrev.
14	Slight	++	+	+++		+	+		+	-	+	Rupture	-
79	-	+++	+	+++		+	+	Relax.	-	+	Rupture	-	Irrev.
80	Slight	+++	+	+++		+	+	Relax.	-	+	Rupture	-	Irrev.
V-62	-	+++	+	+++		+	+	Relax.	-	+	Rupture	+	Irrev.
V-102	Slight	++	+	+++		+	-	Relax.	-	+	Rupture	-	Irrev.
V-104	-	++	+	+++		+	-	Relax.	-	+	Rupture	-	Irrev.

TABLE III. Ultrastructural data: TTC-stained (viable) myocardium. + = present; - = absent. Mod. = moderate

Mitochondria													
Proce- dure No.	Con- fluent cristae	Matrix clearing	Broken cristae	Amor- phous dense bodies	Nuclei		Myofilaments		Oedema		Sarco- lemma	Glycogen	Degree of injury
					Chro- matin clumping	Pycnosis	Con- traction bands	Contr. or relax.	Extra- cell.	Intra- cell.			
90 min occlusion + 2 h reperfusion													
11	Mod.	-	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
70	-	+	-	-	+	-	-	Contr.	-	-	Normal	-	Slight
88	+	-	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
79	-	+	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
80	+	+	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
12	Mod.	-	-	-	+	-	-	Relax.	-	-	Normal	+	Slight
90 min occlusion + 24 h reperfusion													
V-73	-	+	-	-	+	-	-	Relax.	-	-	Normal	-	Slight
V-107	-	+	-	-	+	-	-	Contr.	-	-	Normal	+	Slight
90 min occlusion + 1 week reperfusion													
V-56	+	-	-	-	+	-	-	Relax.	-	-	Normal	-	Slight
V-61	-	+	-	-	+	-	-	Relax.	-	-	Normal	-	Slight
V-62	-	-	-	-	+	-	-	Relax.	-	-	Normal	-	Normal
V-66	+	-	-	-	+	-	-	Contr.	+	+	Normal	-	Slight
V-67	Severe	-	-	-	+	-	-	Relax.	+	+	Normal	-	Slight
V-79	-	Mod.	+	-	+	-	-	Relax.	+	+	Normal	-	Moderate
V-81	-	+	-	-	+	-	-	Contr.	-	-	Normal	-	Slight
V-83	-	+	-	-	+	-	-	Contr.	-	-	Normal	-	Slight

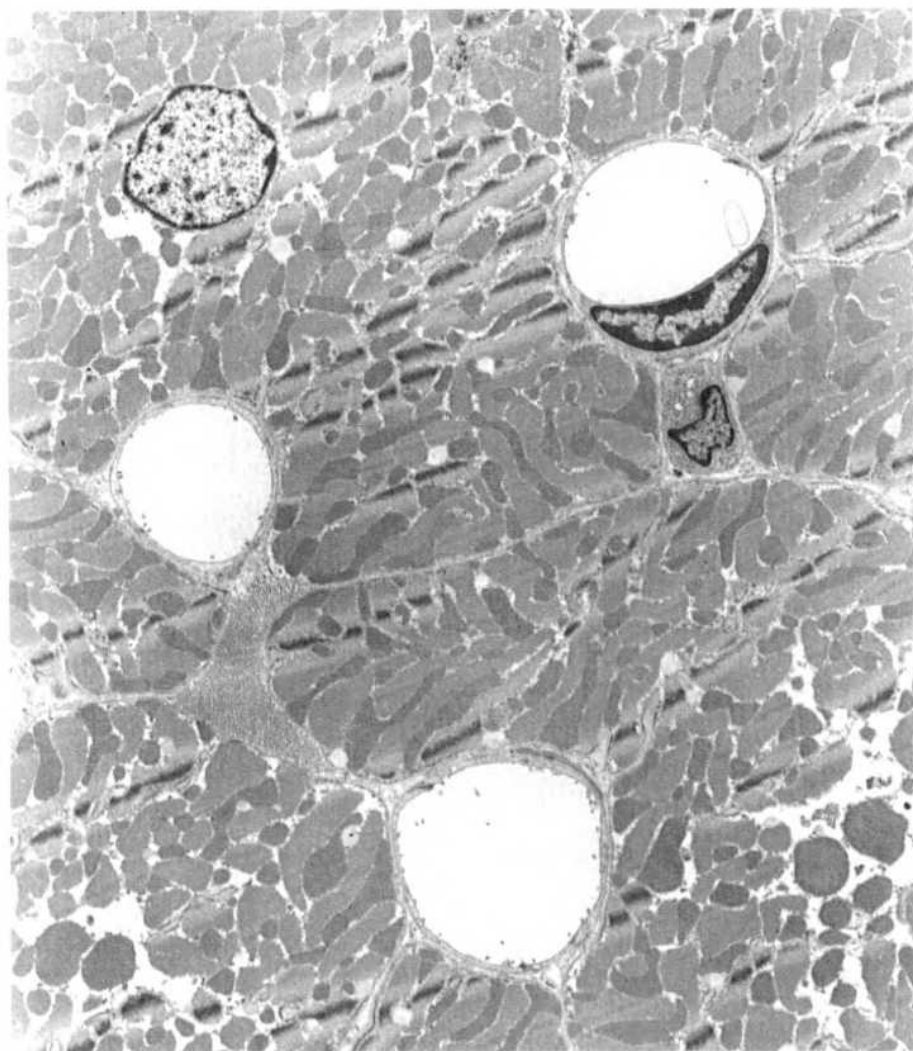


FIG. 1. Normal appearance of the myocardial tissue in a control circumflex area. The nuclear chromatin is evenly distributed. The sarcomeres are arranged periodically and alternate with intact dense mitochondria, capillary vessels are normal and no oedema is seen. (6 mm on figure represents 10 μ m.)

Because of the intracellular oedema, capillary vessels are occluded by extravascular compression and packing of red blood cells occurs. The capillaries are also damaged by the ischaemic insult and become permeable to the red blood cells, causing extravasation of these elements. All these features are shown in figure 2.

All the above mentioned hallmarks of irreversible injury were invariably found in TTC-unstained (infarcted) tissue from 10 dogs (table II) and were absent in TTC-stained (viable) tissue of 16 dogs (table III).

Correlation between the extent of myocardial necrosis and left ventricular function

Macroscopic evaluation of infarct size by the TTC-technique revealed that $11.5 \pm 9.1\%$ (SD) of the left ventricular mass was infarcted after 90 min of occlusion followed by reperfusion. The perfusion area of the occluded LAD was $32.8 \pm 6.5\%$ of the left ventricular mass. This means that about $32.1 \pm 22.8\%$ of the area at risk (i.e. perfusion area of the LAD) became necrotic after 90 min of ischaemia.

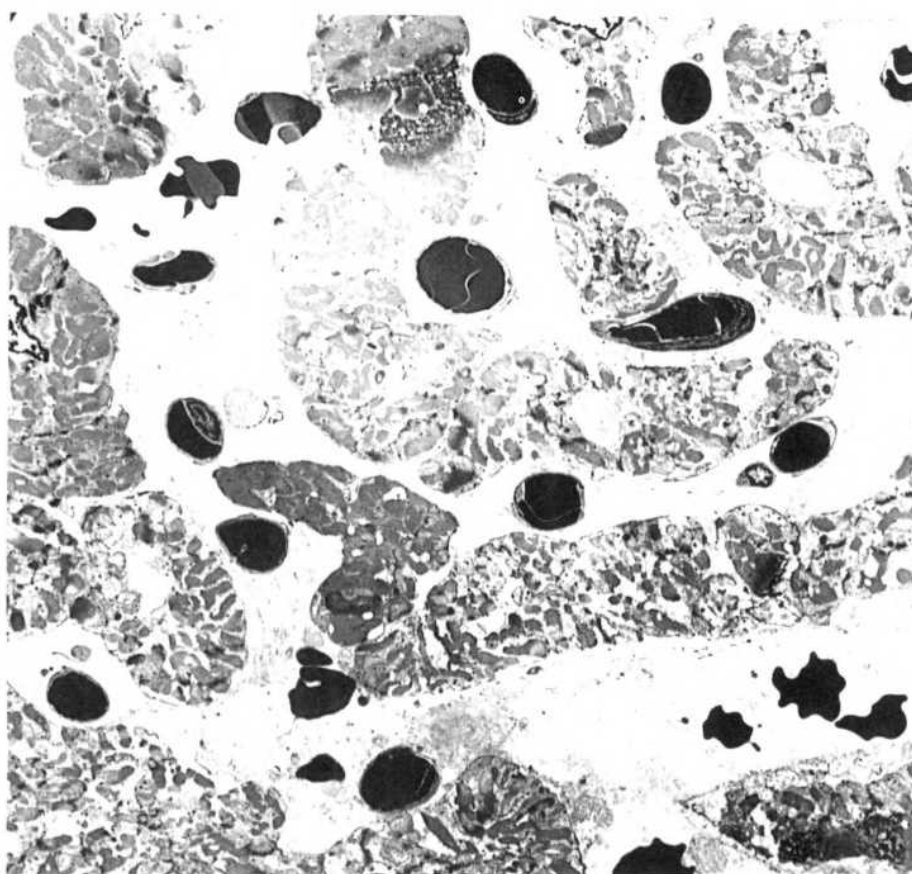


FIG. 2. Irreversibly injured subendocardium after 90 min of ischaemia. The cell nucleus is pycnotic. There is clearing of the mitochondrial matrix and fragmentation of the cristae; numerous intramitochondrial amorphous dense bodies are present. The cell membrane is ruptured; the myofilaments are in relaxation and partially distorted. Oedema is present. Capillary vessels are filled with red blood cells. Some already crenated red blood cells are extravasated. (3 mm on figure represents 10 μ m.)

TABLE IV. Evolution of global ejection fraction and regional segmental shortening (mean values $\pm$ SD). $\dagger$ Paired t test v. occlusion. EF = global left ventricular ejection fraction; RSS = regional segmental shortening of the involved area

	EF	$\dagger P$	RSS %	$\dagger P$
Control	66.9 $\pm$ 10.8	<0.001	33.8 $\pm$ 14.7	<0.001
90 min occlusion	38.8 $\pm$ 10.3		-5.2 $\pm$ 10.3	
150 min reperfusion	30.6 $\pm$ 10.3	< 0.02	-7.7 $\pm$ 14.9	ns
24 h reperfusion	22.8 $\pm$ 10.5	ns	-7.8 $\pm$ 7.0	ns
1 week reperfusion	64.4 $\pm$ 9.2	<0.001	23.2 $\pm$ 12.4	<0.005

Functional assessment of these hearts by left ventriculography showed a depressed global ejection fraction during and after ischaemia (table IV) and regional wall motion showed complete akinesia during the first 24 h to 1 week.

Because the amount of necrosis (expressed as a

percentage of left ventricular mass) varied considerably between experiments, an attempt was made to correlate the percentage necrosis and the reduction in total ejection fraction during ischaemia or after reperfusion. No significant correlation could be found.

TABLE V. *Distribution of collateral blood flow (mean $\pm$ SD) in open chest dogs undergoing 90 min of LAD occlusion followed by reperfusion (ml min⁻¹/100 g). *P < 0.05 v. corresponding normal value*

Normal myocardium (Perfused by circumflex)	Subepicardium	55.6 $\pm$ 22.2
	Subendocardium	68.9 $\pm$ 25.0
	Total transmural	62.9 $\pm$ 23.6
LAD area	Subepicardium	
	Viable	25.6 $\pm$ 19.6*
	Infarcted	2.0 $\pm$ 1.4*
	Subendocardium	
	Viable	32.3 $\pm$ 26.4*
	Infarcted	3.2 $\pm$ 3.6*
	Total transmural	17.2 $\pm$ 17.2*

Viable postischaemic myocardium: histology and quantification

Using the postmortem Evans blue-TTC staining technique, a clear delineation of the perfusion area of the previously occluded coronary artery can be made. The viable tissue in this area is also clearly recognizable by its brick-red colour. Before discussing the histological findings in this zone, it has to be shown that this area belongs to the postischaemic zone or "area at risk" during coronary artery occlusion. This can be shown by the regional blood flow data. After the brick-red area is carefully dissected from the tissue slices, radioactivity can be measured, that is, local flow during ischaemia can be determined. Table V shows clearly that this area was underperfused during ischaemia, although less so than the infarcted, irreversibly damaged part of the perfusion area of the occluded vessel. Most of the viable (brick-red) tissue was localized subepicardially. Upon reperfusion, almost normal flow was restored in this area, while in the infarcted subendocardium a "no reflow" phenomenon was observed.

Electron microscope examination of this postischaemic "viable" myocardial zone revealed no signs of severe (irreversible) damage (table III). There was no rupture of the sarcolemma and no margination of the nuclear chromatin; there were no amorphous dense bodies detected in the mitochondria; there was no oedema and the contractile apparatus was intact; the capillary vessels were not obstructed and had a normal appearance.

Apart from this, some mitochondrial and nuclear changes were observed in viable myocardium which are not among the changes classically described in the existing literature. In viable

tissue samples a confluence or clinging together of mitochondrial cristae was present, accompanied by an increased osmiophilia of these structures. An example is shown in figure 3. The severity of this anomaly in a single mitochondrion was variable, as was the percentage of mitochondria involved. The phenomenon was present in seven of 16 animals subjected to coronary occlusion followed by reperfusion (table III). In control myocardium from the circumflex area, a minimal degree of this confluence of mitochondrial cristae was seen in only two of 10 animals (table I). Also, in viable tissue the myocyte nucleus invariably showed some degree of chromatin clumping instead of the normal uniform chromatin distribution. An example is shown in figure 3. Here nuclear changes were present in only one of the 10 dogs in which control circumflex myocardium was analysed. The significance of these nuclear and mitochondrial changes in viable myocardium remains to be determined. Data on viable reperfused myocardium stem from investigations in which the duration of ischaemia was limited to a time interval known to produce only reversible injury [4, 5]. The evolution of ultrastructural changes in viable myocardium that has been subjected to prolonged episodes of ischaemia followed by periods of reperfusion is largely unknown.

Relationship between myocardial function and histology in postischaemic viable myocardium

Local segmental wall motion was calculated from left ventricular angiograms taken at the end of 90 min of LAD occlusion and at 150 min, 24 h and 1 week of reperfusion (table IV). During occlusion and up to 24 h after reperfusion, total akinesia of the anterior wall was found in spite of

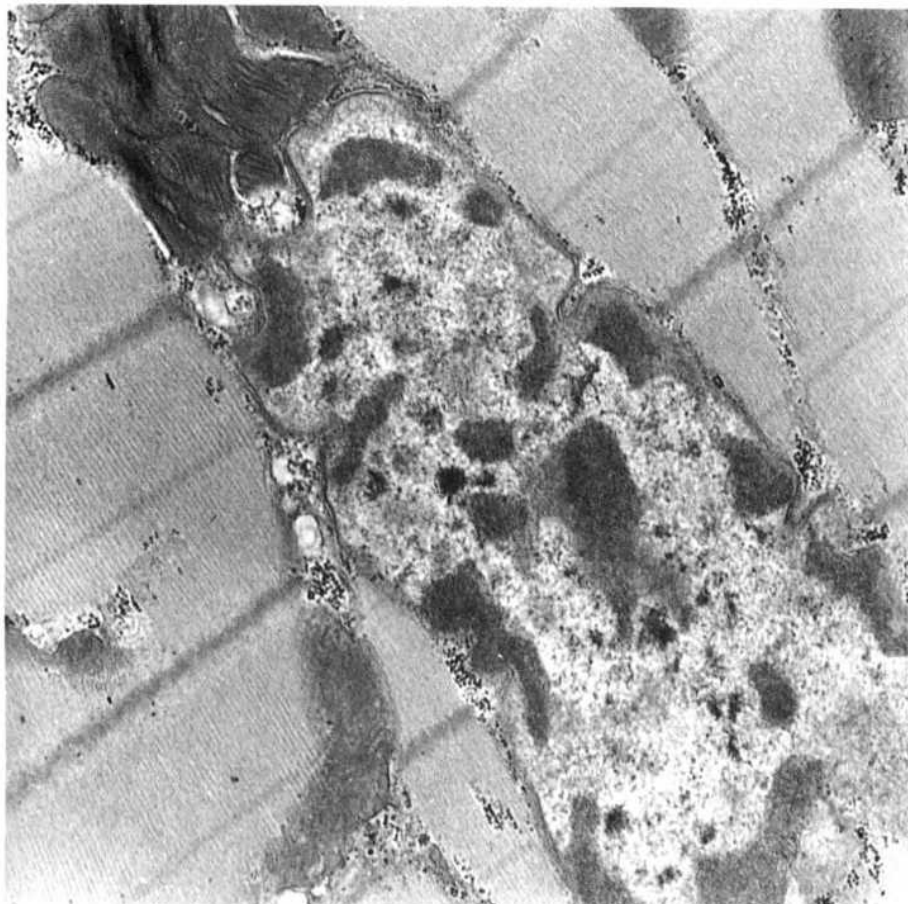


FIG. 3. Viable subepicardium after 2.5 h of reperfusion following 90 min of ischaemia. The appearance of the contractile system and the mitochondria is essentially normal. Some mitochondria show a condensation of cristae. The nucleus shows some degree of chromatin clumping, but is not pycnotic. Note the complete absence of oedema. (15 mm on figure represents 10 μ m.)

the fact that 68% of the perfusion bed of the occluded artery remained viable. After 1 week of reperfusion, partial recovery of segmental wall motion was obtained. As mentioned in the previous section, only very minor structural anomalies were found in this viable, non-contractile myocardial zone. This zone regained its function spontaneously after 1 week of reperfusion. At this time histology remained unchanged compared with the early reperfusion phase.

DISCUSSION

By detailed assessment of subcellular myocardial structure during progression of ischaemia, a clear sequence of morphological changes can be described. After a few minutes of ischaemia, the first

subtle morphological alterations are found in the mitochondria: the small osmiophilic granules embedded in the mitochondrial matrix disappear. When ischaemia proceeds, more pronounced alterations occur in the mitochondria: clearing of the mitochondrial matrix, swollen and disrupted cristae, and rupture of inner and outer mitochondrial membrane. These lesions can be used to create a scoring system for the semi-quantitative grading of ischaemic injury. However, when ischaemia passes the "point of no return" in terms of cell viability, a clear morphological picture is found: disruption of the sarcolemma, inclusion of typical amorphous dense bodies in the mitochondria, intracellular oedema, and chromatin clumping and margination in the nucleus. It is remarkable that, under all these conditions,

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the contractile system (sarcomeres and myofibrils) remains structurally intact as far as can be detected with the electron microscope. Only at a late stage after the onset of irreversible damage, does the contractile system disintegrate.

It is obvious that irreversibly damaged myocytes are, and remain, non-functional. There is, however, no direct relation between the amount of myocardial cell necrosis and the degree of global myocardial dysfunction. This can be explained by the compensatory increase in function of the contralateral, normal myocardium. This is the first hint that, although close correlates can be found between the histology and the degree of ischaemic insult, no correlation will be found between postischaemic function and quantitative and qualitative assessment of histological alterations. Indeed, viable postischaemic tissue will be non-contractile for hours to days while ultrastructure reveals only very minor abnormalities. This phenomenon is called "myocardial stunning" [1]. Although structure and function are not related in the postischaemic state, assessment of fine structure has a definite prognostic value in terms of recovery of function after a certain degree of myocardial ischaemia. Non-contractile postischaemic myocardium will regain its function spontaneously after a variable time delay, provided histological criteria of viability of the tissue remain. However, it may be concluded that myocardial histology is not a reliable index of postischaemic myocardial function.

SUMMARY

The relation between the histology of the myocardium and left ventricular function was studied in 23 dogs submitted to 90 min of coronary artery occlusion followed by reperfusion for up to 1 week. It was shown that 32% of the perfusion area of the occluded coronary artery was irreversibly damaged. There was, however, no significant

correlation between the decrease in left ventricular function (ejection fraction assessed by angiography) and the extent of myocardial necrosis.

Upon reperfusion, salvage of 68% of the perfusion area of the occluded vessel was obtained. Viability of the myocardium in this area was demonstrated by electron microscopy. However, postischaemic regional function was completely lost in the first 24 h, in spite of this considerable amount of viable tissue. Nevertheless, regional function recovered after 1 week of reperfusion, which suggests a stunned myocardium in the early postischaemic phase.

These results show that histological examination of postischaemic tissue has prognostic value in terms of recovery of function, but a direct correlation between structure and function does not exist in the early reperfusion phase.

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BIOCHEMISTRY: INDEX OF THE FUNCTIONAL STATE OF THE HEART?

W. ISSELHARD

Twenty-five years ago, in an era when a large number of specific assays were being developed, it was believed that biochemical measurements could provide an index for the functional state of the heart. For example, it had been shown that the rapid deterioration in function in the asphyxiated animal was associated with the rapid breakdown of creatine phosphate (CrP) and a continuous decrease in ATP [8, 11]. The changes were assumed to be attributable to inadequate energy production in anaerobiosis, and it was known that the changes could be reversed providing that the limit of tolerance for anaerobiosis had not been exceeded. However, more recent work has suggested that the relationship between myocardial metabolism, in particular the myocardial status of energy-rich substrates and phosphates, and myocardial function, is not as clearly defined as had been thought.

"NORMAL" METABOLIC STATUS AND FUNCTION OF THE HEART

In the normally perfused and functioning heart, there is a pool of adenine nucleotides (5-7 $\mu\text{mol/g}$ wet tissue) with ATP being by far the largest fraction. The energy charge potential ($\text{ECP} = (\text{ATP} + 0.5 \text{ ADP}) / (\text{ATP} + \text{ADP} + \text{AMP})$) has a high value of about 0.9. The tissue concentration of total creatine (TCr) is two to four times higher than that of the adenine nucleotides; between 35 and 50% of TCr is phosphorylated to creatine phosphate (CrP). In the unstressed myocardium of animals, the ratio CrP:ATP exceeds the value of 1. The human myocardium is usually reported to have smaller concentrations of tissue CrP and TCr, and of the ratios CrP:TCr and CrP:ATP, than those found in laboratory animals. The normal myocardium is rich in glycogen. The

tissue concentrations of the intermediates of the glycolytic system and of lactate are low.

The tissue concentrations of many substrates, metabolites and enzyme activities vary in different regions of the heart. For example, there are differences between atrial and right or left ventricular myocardium, between epi- and endomyocardial layers, and between basal and apical areas of the ventricles. There are also some quantitative variations between the hearts of different species. In addition, there are inter-individual variations and concentrations vary with factors such as age, season of the year, special diet, withdrawal of food, stress, experimental or operative manipulations, and the method of tissue sampling and preparation, as well as the method of assay. Anaesthesia induces a variety of alterations, including those in metabolism. However, the myocardial status of energy-rich phosphates of otherwise unstressed hearts is only little affected by pentobarbitone, hexobarbitone, thiopentone (with or without nitrous oxide), ether, chloralose plus urethane, or halothane, during anaesthesia of up to 9 h duration in rabbits [1]. The analysis of metabolite patterns and their changes yields better information than a measurement of one or two single substances.

Steady state tissue concentrations of substrates and metabolites reflect an equilibrium between synthesis and supply on the one hand, and demand and utilization on the other. There is a high degree of coupling and a massive disturbance on either side will render steady states impossible. Under physiological conditions, and under certain pathological situations which have not progressed beyond a critical point, the steady state is not a fixed one, but changes with the loads on the cells of the heart. It is well established today that myocardial load and energy demand affect the myocardial metabolic status of the "normal" heart. For example, in the heart-lung preparation of guineapigs, Hochrein and Döring demon-

strated as early as 1960 [5] that left ventricular work load and CrP concentration are inversely correlated in a quasi-linear manner, and that the CrP concentration is influenced about 2.5 times more by changes in pressure load than by alterations in volume load. Changing the pressure-volume load by a factor of 10 by varying the volume load caused the concentration of CrP to vary between 6 and 12 $\mu\text{mol g}^{-1}$, while the ATP concentration changed by only 5%. In a compilation of data obtained in canine hearts by several research groups, Kübler [12] demonstrated a similar inverse relation between the myocardial status of energy-rich phosphates and myocardial oxygen consumption, which may be used as a criterion of the myocardial energy demand and which varied between 12 and 0.5 ml $\text{min}^{-1}/100 \text{ g}$. The change in the CrP concentration averaged 6 $\mu\text{mol g}^{-1}$, and was related in a non-linear manner to the oxygen consumption. The ATP concentration changed by about 20%. Clinical medicine takes advantage of this fact, for example in cardiac surgery, when hearts are arrested by means of cardioplegic perfusion of several minutes' duration at low temperature under aerobic conditions. While the adenylic acid system shows only a tendency towards an improvement, the CrP concentration is drastically increased with that of TCr remaining constant.

In the normal heart, high concentrations of CrP usually reflect a low energy demand of myocytes, but also result from a so-called "utilization insufficiency," irrespective of the energy demand.

"ALTERED" METABOLIC STATUS AND FUNCTION OF THE HEART

In the search for relationships between metabolism and function, it is pertinent to enquire how myocardial function is affected by deviations from the regular metabolic status, and what are the consequences of a deterioration in metabolic status? Clinically, the most important situations are those resulting from an inadequate oxygen supply.

Critical hypoxia, asphyxia, and critical incomplete or complete ischaemia result in massive alterations in function, metabolism and morphology. Although there are certain differences in the consequences of these pathophysiologically different situations, the ultimate cause for the failing and finally the cessation of any kind of function,

and for the structural derangements, is an inadequate energy production in anaerobiosis. The myocardium has a remarkable glycolytic energy capacity, but glycolytic energy production cannot substitute for aerobic energy supply. Depending on the situation, anaerobic energy production and distribution are limited by the availability of utilizable substrates, by a critical reduction of energy-rich phosphates, by an increasing tissue acidosis, or by the accumulation of inhibitory substances. Common to all situations is the drastic change in the metabolic status as compared with the regular pattern. It is characterized by a breakdown of CrP, a decrease in ATP and possibly a temporary increase in ADP, AMP and degradation products of the nucleotides, a continuous reduction of adenine nucleotides, a decrease in glycogen, and an accumulation of lactate. Heavy or long lasting deprivation causes a loss of TCr, which is possibly indicative of irreversible damage of myocytes.

There is some doubt concerning the functional capacity of the myocardium following anaerobic situations which result in persistent alterations of the metabolic pattern. The rate and extent of recovery of the metabolic status are in many cases a function of the degree of the ischaemia-induced alterations, but there may be prolonged recovery periods even though the loading had clearly been within the tolerance limits. The CrP concentration is usually restored rapidly, and often overshoots. Markedly depleted glycogen stores are replenished within a few hours, but the restoration of ATP and the pool of adenine nucleotides may take many days. This is especially true if the adenine nucleotides had been degraded beyond adenosine during anaerobiosis, and the degradation products have been washed out. After 30 or 60 min occlusion of the anterior descending branch of the coronary artery in canine hearts, with a reduction of the ATP concentration to 58% or 39%, and of the sum of the adenine nucleotides to 66% or 48% respectively, the restoration of normal values took about 14 days [9].

In the isolated working heart or the paced septal preparation, a large body of results show a linear relationship between the degree of alteration of the metabolic status and the extent of depression of various functional parameters. These include: aortic flow as a function of the tissue concentration of ATP plus CrP [4] and tissue ATP in relation to (a) ventricular power (calculated as the product

of the aortic flow times the difference between the aortic and left atrial pressure) [15], (b) maximal rate of tension development [14], (c) coronary and aortic flow rate, heart rate and developed aortic pressure [7]. In one and the same experimental preparation the extent of depression of different functional parameters may vary considerably with a given tissue concentration of ATP [7]. As a rule, the hearts had been damaged globally by ischaemia, anoxia or special perfusion techniques.

A relationship between metabolic acidosis and function has also been described in the heart *in vivo*. For example, Hayashi and colleagues [3] have shown a relationship between reduction in coronary blood flow produced by graded coronary artery constriction, regional myocardial contraction, and the local tissue concentration of ATP. Similarly, it has been shown that there is a correlation between the rate of recovery of ATP and the adenine nucleotide pool, and the restoration of functional parameters after regional myocardial ischaemia [15, 16].

In summary, it is not surprising that some people interpret the statistical correlation between myocardial metabolic status and functions as a cause-and-effect relationship. However, the significance of such a relationship should be considered critically for several reasons. First, individual variations between metabolic parameters such as ATP, ATP+CrP, CrP, adenine nucleotide pool, and the functional parameters are large. The linear relationships are only derived by mathematical handling of data, and the correlation coefficients are not always convincing. Second, functional performance does not depend on energy supply alone, but is influenced by a large variety of factors such as electrolyte milieu, pH, hormones, substrate supply, etc. Third, tissue concentrations do not reflect the turn-over of substrates and metabolites and thus the availability of biologically utilizable energy. Fourth, the myocardial cell must be seen as a compartmentalized entity in terms of its functional performances and energy-generating systems. Fifth, an increasing body of evidence has shown that there is not necessarily a correlation between the status of energy-rich phosphates and functional performance.

During post-asphyxial recovery, hearts may perform normal or increased pressure-volume work, although the tissue concentrations of ATP and adenine nucleotides are below the normal ranges and the CrP concentration is increased

above the normal value [8]. After induced cardiac arrest, post-ischaemic functional recovery improves progressively within a short time without concomitant changes in the over-all metabolite pattern [10]. After cardiac arrest, induced by various methods, post-ischaemic functional recovery may be different despite an identical myocardial metabolic status [10]. Recovery of function after cardiac arrest may be influenced independently of the tissue concentration of ATP by a variety of factors, such as the use of normal blood or substrate-enriched blood or perfusate, reduction of Ca^{2+} -activity in the perfusate, secondary cardioplegia, or reduction of the after-load in the early recovery phase [17]. During regional ischaemia or post-ischaemic reperfusion, an individual correlation between ATP concentration and segmental function of the myocardium could not be demonstrated [19]. Data are available which show that there is no close relationship between the post-ischaemic ATP concentration and the degree of dysfunction on the one hand, and the rate of recovery of both function and nucleotide pool on the other hand [6]. Although a close correlation existed in the heart between the rate of ultrastructural, functional and metabolic deterioration at the end of an ischaemic period, during reperfusion the restoration of cardiac function and of high energy phosphate metabolism occurred at a slower rate than the reconstitution of cellular structures [18].

"CRITICAL DETERIORATION" IN METABOLIC STATUS AND FUNCTION OF THE HEART

When considering the potential relationship between function and metabolism or metabolic status, it is important to consider whether there is a critical metabolic status beyond which there is no return of function. It is generally agreed that the post-anaerobic recovery of many or possibly all aspects of cellular performance is an exponential function of the duration, extent, or both, of the anaerobiosis-induced alterations. This implies that, beyond a "borderline" situation, the recovery period will be infinite. Since life support devices can only take over organ function for a limited period of time, it is important to restrict the alteration of organ function to such a degree that a reasonably short recovery period is possible.

Bretschneider [2] suggested that canine myocardial tissue concentrations of ATP and CrP of about 4 and 2 $\mu\text{mol g}^{-1}$ wet weight were the limit

beyond which the myocardial metabolic status should not be altered. It might be considered helpful to define a certain metabolic pattern when comparing various experimental loads under otherwise similar conditions in one species, but it is not possible to generalize concerning absolute values. First, the metabolic status differs quantitatively in various species under normal conditions and, second, CrP is usually restored rapidly and a reduction to zero values during anaerobiosis does not preclude rapid restoration within a few minutes. Third, data have been published which show that hearts *in situ* have resumed and maintained circulatory performance with a heavily altered metabolic pattern. A 30–40% reduction in tissue ATP and total adenine nucleotide concentrations seems to be tolerable during the early post-ischaemic recovery phase [13]. Complete post-ischaemic restoration of cardiac function has been described in hearts with a tissue concentration of ATP at the end of ischaemia and post-ischaemia reperfusion of about 1.2 and 2 $\mu\text{mol g}^{-1}$, respectively, if appropriate measures were taken in the early recovery phase. However, hearts with ATP concentrations of about 2.1 and 2.8 $\mu\text{mol g}^{-1}$ recovered poorly if blood was used for reperfusion [17].

There is certainly a critical tissue concentration of ATP or a critical ATP concentration at the sites of various functions within the cell. However, these critical concentrations will vary with the method used, with the skill of the investigator, and with the increase in knowledge of the pathophysiological processes in the anaerobic and post-anaerobic heart. It is, therefore, probably better to characterize the potential for return of function according to the possibility of rapidly normalizing the ECP, restoring a normal tissue concentration of CrP, and rapidly eliminating tissue acidosis in situations in which the tissue concentration of TCr has not been reduced massively.

SUMMARY

The description of metabolic patterns during well defined conditions has been, and will be, a very helpful tool in characterizing reactions of cells, tissues and organs to physiological and pathophysiological situations. As a rule, the measurements yield global values. Discrimination between the integrity of different cellular compartments and individual cell functions is difficult and possible only in particular circumstances. Metabol-

ism is not a static, but a dynamic cellular activity. Status analyses are like stills from a movie. With the present state of the art, however, it seems neither possible nor justified to describe or predict functional performance of the heart using analyses of metabolism, which can be performed simply, rapidly, reliably and with general validity. The best way to assess functional performance is to measure function!

Metabolism and metabolites are the fuel and constituent parts of structure and its functions. Because of this, there must be a link between function, structure and metabolic activities and metabolite patterns. The successful symptomatic therapy of myoadenylate deaminase deficiency in patients by administration of ribose [20, 21] is just one good example of the relation between metabolism and function, and of the value of subtle studies of metabolism and analyses of metabolic patterns in animals and in man.

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THE ISOLATED HEART PREPARATION

R. G. MERIN

There are two basic reasons why the isolated heart has been used to study the effects of anaesthetics. In the first place, the use of an isolated heart allows precise control of the determinants of myocardial function: preload, afterload, heart rate and the perfusate. Second, the isolated heart allows investigation of cardiac metabolism to a much more controllable degree than does the intact animal. There have been two general methods for isolating the heart from the rest of the body. Perhaps the more physiological technique involves the heart-lung preparation as described by Knowlton and Starling [13]. A more modern adaptation has been the study of both animals and man during cardiopulmonary bypass. This topic is the subject of another paper in this issue and will not be considered further. The second, more simplistic, way of isolating the heart is merely to excise it from the body of the animal and then perfuse it, usually with a blood-free salt and nutrient solution.

THE HEART-LUNG PREPARATION

Among his many contributions to cardiovascular physiology and pharmacology, E. H. Starling [13] introduced the isolated heart-lung preparation (fig. 1). The technique was certainly an invasive one! The heart was isolated *in situ* so that the inflow (vena cava) was supplied from a reservoir the height and volume of which could be adjusted. The outflow (aorta) was directed through one of the early Starling resistors so that the resistance to outflow could also be either maintained constant or adjusted as desired. In the more modern preparations either ventricular or atrial filling pressures are measured or controlled, the inflow is usually controlled by the height of the reservoir, the outflow is adjusted to the resistor, and cardiac output measured by either timed collections from

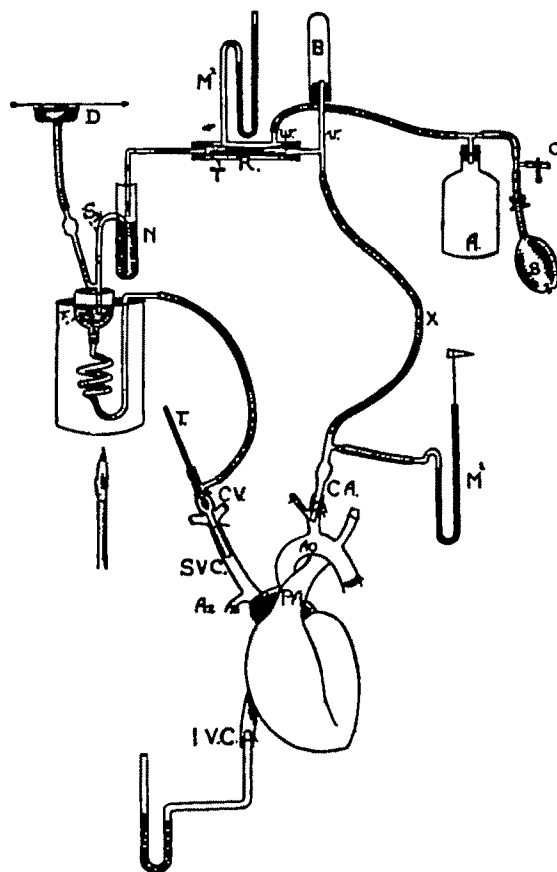


Fig. 1. Schematic diagram of Knowlton-Starling (1912) heart-lung preparation [13].

the resistor or, in some cases, flow probes on the aorta. The animal's lungs serve as the oxygenator and, in the case of inhalation anaesthetics, as the route of administration of the drug. For non-inhalation drugs, appropriate concentrations are added to the venous reservoir. This preparation lends itself very well to the concepts of the Frank-Starling volume control of cardiac contractility and indeed, after the primitive experiments of Otto Frank using isolated frog hearts,

was the major preparation in which this relationship was demonstrated.

Although the heart-lung preparation does allow for the control of the determinants of cardiac function, responses to cardiodepressant drugs are exaggerated for two reasons. First, the body's normal reflex responses to cardiac depression are specifically and intentionally inhibited. Second, the preparation is traumatic and cardiac function is probably depressed to begin with. For example, in one of the most cited studies of the effect of anaesthetics on cardiac function, the heart-lung preparation was often supported by an infusion of adrenaline [21]!

Anaesthetic experiments using the heart-lung preparation

Among the earliest publications of the effect of anaesthetics on cardiac function using a heart-lung preparation were those in 1949 of Moe and colleagues [16] and Woods and colleagues [27] who, respectively, showed dose-related depression of cardiac function, by cyclopropane and by the two ultra-short acting barbiturates, thiopentone and thiamylal. In the first comparative study, Fisher, Bennett and Allahwala [7] investigated the effects of chloroform, diethyl ether, cyclopropane and divinyl ether on the Starling heart-lung preparation, and reported that chloroform was the most depressant and that diethyl ether produced a dose-related depression, whereas cyclopropane and divinyl ether were reported to have less effect. On this side of the Atlantic, Prime and Gray [22] also compared ether and cyclopropane as well as investigating thiopentone and two new neuromuscular blocking drugs, gallamine and decamethonium. They observed marked depressant effects by thiopentone and cyclopropane (in only 3–5% concentration) with a dose-dependent depression by diethyl ether similar to that reported by Fisher, Bennett and Allahwala [7]. No depression was seen with the neuromuscular blockers. Price and Helrich [21] also compared cyclopropane, diethyl ether and thiopentone, but further looked at the effect of hydrogen ion and nitrous oxide. They confirmed Prime and Gray's results [22] showing a dose-related depression in the ratio of cardiac output to right atrial pressure by ether, nitrous oxide, cyclopropane and thiopentone. They attempted to equate anaesthetic concentrations with this depression, and suggested that, for light surgical anaesthesia, cyclopropane, ether and nitrous oxide all produced

about a 50% depression in cardiac function, whereas thiopentone produced only a 30% depression. In a rather scantily documented report to the Council on Drugs considering the new anaesthetic, halothane, Burn and colleagues [2] also studied the effect of chloroform, ether, trichloroethylene and halothane on the Starling heart-lung preparation. They reported that halothane and chloroform produced a relatively equivalent dose-dependent depression of cardiac output, whereas both diethyl ether and trichloroethylene showed little effect at anaesthetizing concentrations. However, it is of some note that they administered the latter two anaesthetics for only 10 min, not realizing the importance of high blood solubility of these two agents as far as organ system effect was concerned. Finally, Flacke and Alper [8] reported that 0.25 and 0.5% halothane had little effect on cardiac function, but 1% produced a rapid and severe decrease in cardiac output, with simultaneous increases in right atrial and left atrial pressure. They also reported that reserpinized dogs responded in the same fashion and that an infusion of noradrenaline was able to reverse completely the effects of concentrations of halothane as great as 1.5%, but that higher concentrations, even in the presence of noradrenaline, resulted in depression of cardiac function.

These experiments established the principle that all potent inhalation anaesthetics are direct dose-dependent cardiac depressants in the dog heart-lung preparation. The relatively minor effects of diethyl ether and cyclopropane in intact animals then suggest that either hormonal or central nervous system effects produced by these anaesthetics modify the direct cardiac depressant effects.

EXCISED PERFUSED HEART

Some of the early experimenters in cardiovascular physiology merely excised animal hearts, placed them in a dish containing saline and observed their beating response to various interventions. One of the first investigators to standardize an excised heart preparation, in 1895, was Langendorff [14] and, indeed, his preparation became a standard, recognized even to this day (fig. 2). Langendorff suspended the excised rat heart by its aortic cuff on a hollow metal tube connected via a stopcock and flexible tubing to a perfusion system which allowed control of perfusion

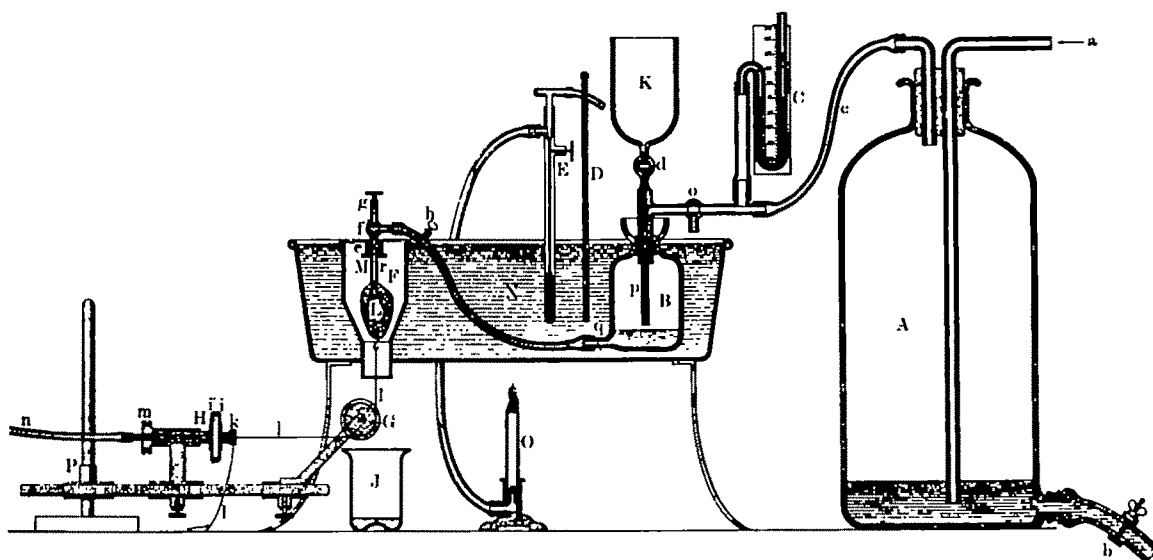


FIG. 2. Copy of original engraving of the Langendorff (1895) preparation [14].

pressure and composition of perfusate. Function of this heart was measured by a hook in the apex connected to a lever system recording on a smoked drum which documented the displacement of the apex with each beat. A temperature-sustaining water jacket completed this relatively simple preparation. Major advantages of the Langendorff preparation were its simplicity and relative stability as long as the proper perfusate and perfusion pressure were maintained. However, this was a distinctly unphysiological preparation, for the heart in fact did not function as a pump, nor was there real preload. Subsequent modifications have introduced a fluid filled balloon to the left ventricle so that there was some sustained preload. In addition, this balloon allowed the measurement of developed pressure as well as the rate of pressure development (dP/dt). Nevertheless, this was a relatively low work type preparation and, in particular, measuring ongoing metabolic performance of this heart was difficult. The major metabolic measurements that could be made used rapid "freeze clamping" of the heart for measurement of tissue metabolites, particularly the high energy phosphates.

Seventy years ensued before different workers attempted to produce a more physiological isolated heart preparation. One of the more widely accepted of these has been that developed by Neeley and colleagues [17] whereby, not only was

the heart suspended by the aorta, but the left atrium was cannulated also (fig. 3). Now, the heart actually pumped the perfusate using a "wind-kessel" type of aortic outflow resistance and cardiac output could be documented. In addition, it was possible to manipulate atrial and ventricular volumes and pressures and produce cardiac function curves similar to those obtained in the heart-lung preparation (fig. 4). Another modification also cannulated the pulmonary artery for measurement of oxygen consumption and ongoing metabolites without killing the heart by freeze clamping. However, this preparation was much more technically demanding and of limited stability (2 h), so that use of the Langendorff preparation continued even after development of this working heart preparation.

However, even more than the heart-lung preparation, the isolated perfused heart was unphysiological. Obviously, only effects on the heart itself could be measured (the object of the preparation, after all!). Until the development, in recent years, of oxygenators for blood-perfused systems, blood-free perfusates were used. This limited the oxygen carrying capacity so that coronary blood flows were much greater than in the intact animal. However, these hearts were not ischaemic if properly prepared. The oxygen tension in the coronary effluent was consistently greater than 13 kPa; the hearts responded normally to changed

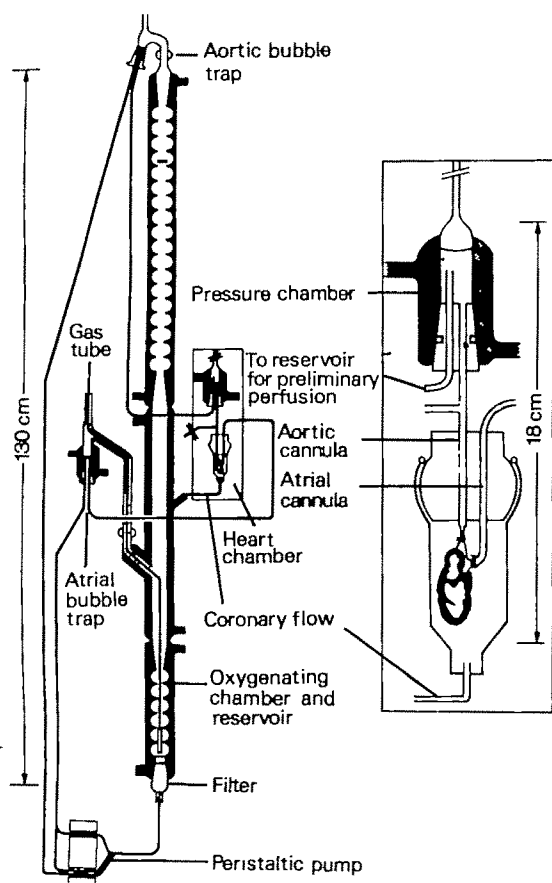


FIG. 3. The Neely (1967) working rat heart preparation [17].

myocardial oxygen demand situations; induced ischaemia produced functional and metabolic changes identical to those observed in intact animals; and finally, the high energy phosphates, the ultimate result of adequate oxygenation, were present in amounts similar to those seen in intact animal hearts [18]. Many manipulations can improve the quality of these hearts, including nutrient content of the perfusate, harvesting techniques, temperature, etc. Of course, the relevance of data in one species for results in another must be viewed with some caution, especially as regards clinical management. Nevertheless, the isolated perfused working heart can provide valuable insights to the cardiac pharmacology of anaesthetic drugs.

Although there were a number of workers around the turn of the century who looked at the effect of diethyl ether and chloroform on various

excised hearts, most of these descriptions were sketchy and very difficult to interpret. For example, Sherrington and Sowton [26] reported experiments in the excised gorilla heart! According to their description, chloroform $100 \text{ mg litre}^{-1}$ produced a "90 % reduction of the beat," whereas with $750 \text{ mg litre}^{-1}$ "the beat was extinguished temporarily." They also noted "resistance to chloroform has been somewhat greater in this heart than that shown previously in the cat's heart." Not even a kymograph tracing was presented.

Anaesthetic experiments in excised perfused hearts

Langendorff. In 1962, Asher and Fredrickson [1] compared the effects of chloroform and halothane in a Langendorff rabbit heart preparation. They reported that the two anaesthetics produced an equivalent dose-dependent depression in function of this isolated heart, confirming the sketchy observations of Burn and colleagues [2] in the heart-lung preparation. Paradise and Bibbins [19] compared the effects of diethyl ether, chloroform, halothane and methoxyflurane in a Langendorff rat heart preparation. Like Price and Helrich [21], they tried to equate anaesthetic concentrations with cardiovascular depression. They reported that diethyl ether and methoxyflurane produced the least cardiac depression compared with the concentrations necessary for anaesthesia, halothane was intermediate and chloroform was the most depressant to the function of the isolated perfused rat heart. Kissin's group at the University of Alabama [11] and Wechsler's cardiovascular surgery laboratory at Duke University [9, 10, 20] were looking at both metabolic and functional effects of anaesthetics using a Langendorff preparation. Wechsler's group was primarily interested in the modifying effect of anaesthetics (and other drugs) on the ischaemic rat heart. In a series of investigations (only one of which [9] is published in other than abstract form), they showed that the three clinically available inhalation anaesthetics halothane [20], isoflurane [9] and enflurane [10] had little effect on the pre-ischaemic tissue content of high energy phosphates, the time required for ischaemic contracture to develop or the tissue content of high energy phosphates at the time of ischaemic contracture. In the isoflurane and enflurane experiments, the hearts were also reperfused after ischaemia and both anaesthetics increased the percent recovery of pre-ischaemia

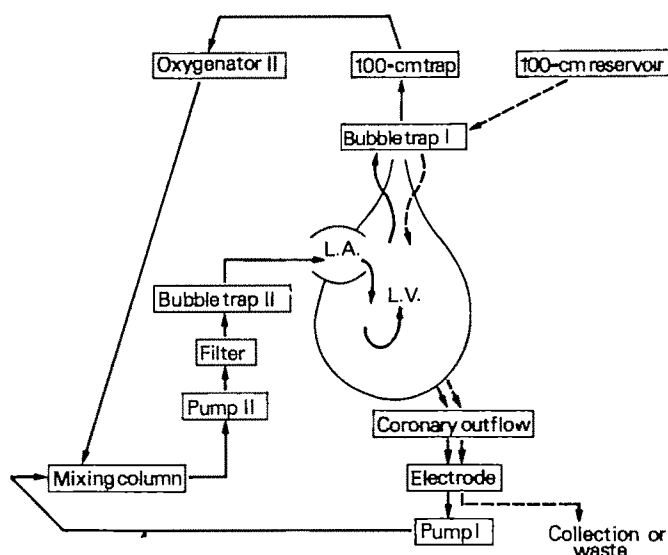


Fig. 4. Schematic diagram of Ross (1972) working rat heart preparation [25].

developed pressure as well as tissue content of high energy phosphates. The same was also shown for the calcium channel blocker, nifedipine but, interestingly enough, there was no additive effect of the combination of nifedipine and enflurane [24].

Kissin's laboratory was also interested in the metabolic effect of anaesthetics, but they used a different approach. Using surface fluorimetry on a rat heart, they demonstrated that the three currently used inhalation anaesthetics and diethyl ether all produced an increase in myocardial reductive metabolism (NADH/NAD) [11]. At calculated equi-anaesthetic concentrations, ether produced the most increase in NADH, with enflurane intermediate and halothane or isoflurane producing the least. At anaesthetic concentrations producing a 50% decrease in cardiac function (dP/dt), ether and halothane produced the least increase in NADH, again with enflurane intermediate and isoflurane producing the most. In a companion study [12] in which a rabbit heart was used, the NADH production by halothane was shown to be a fraction of that produced by ischaemia and, when halothane was administered to the ischaemic heart, there was slightly less NADH production for an equivalent degree of ischaemia, suggesting that halothane at least did not aggravate the ischaemic production of NADH. The other thrust of the Kissin group in using the Langendorff rat heart was to look at

drug interactions. Marshall and colleagues [15] showed that the interaction of halothane and nifedipine on the function of the isolated rat heart was mostly additive, and Reves and co-workers [24] indicated that the interaction of diazepam and fentanyl was also additive.

Working heart. In their 1982 abstract [20], Wechsler's group also looked at the effect of halothane on a working rat heart preparation. They showed that 1.5% halothane produced a significant decrease in cardiac output and the product of cardiac output times mean arterial pressure at 5, 10, and 15 mm Hg left atrial pressure, thus confirming previous observations in both heart-lung preparations and intact animals concerning the negative inotropic effect of halothane. However, most of the anaesthetic experiments using the excised perfused working rat heart have come from our laboratory at the University of Texas Medical School in Houston, headed by Dr Leslie Cronau. In continuing experiments so far published only in abstract form [3-6], we have shown that halothane produces a dose-related depression in cardiac function while also decreasing glycolytic flux [5]. When insulin was added to the glucose in the perfusate, essentially the same functional depression was seen, but glycolysis was somewhat less depressed [4]. Bupivacaine in equi-anaesthetic concentrations produced significantly more depression of the

TABLE I. Effects of halothane (H) and isoflurane (I) on working rat heart (mean values $\pm$ SD). *P < 0.05 v. control; †P < 0.05 v. 0.8% halothane or 1.2% isoflurane

	Control	0.8% H	1.2% I	1.6% H	2.4% I
MAP (mm Hg)	81.9 ± 17	65.2* ± 19	79 ± 16	49.1*† ± 10	60.9* † ± 13
Cardiac output (ml min ⁻¹ g)	53.5 ± 7.5	45.5* ± 13	56.7 ± 12	38.7*† ± 10	49.5 ± 10
Heart rate (beat min ⁻¹)	259.1 ± 40	238.4 ± 68	246.1 ± 28	246.5 ± 48	238 ± 33
Coronary flow (ml min ⁻¹)	16.05 ± 4	13.5* ± 5	16.4 ± 4	11.2*† ± 5	13.6 ± 5
MAP $\times$ CO	44.7 ± 4	31.7* ± 15	46.1 ± 17	19.8*† ± 8	31.2*† ± 14
O ₂ consumption (mol min ⁻¹ g)	8.2 ± 0.6	5.3* ± 0.3	7.8 ± 0.6	3.6*† ± 0.3	5.8*† ± 0.4
Glucose uptake (mol min ⁻¹ g)	2.67 ± 0.2	2.21* ± 0.2	2.67 ± 0.3	2.09* ± 0.1	2.1*† ± 0.2
Tissue glycogen (mol g ⁻¹)	102 ± 3	98 ± 3	87 ± 6	76* ± 7	84* ± 8
Lactate production (mol min ⁻¹ g)	1.69 ± 0.12	1.43 ± 0.4	1.51 ± 0.3	1.98 ± 0.2	1.31 ± 0.1

isolated working rat heart than did lignocaine [3]. However, lignocaine appeared to impair glycolytic flux more than bupivacaine. Finally, we have been investigating the comparative effects of halothane and isoflurane on function and metabolism in the isolated working perfused rat heart [6]. At equi-anaesthetic concentrations, halothane produced significantly more depression of cardiovascular function (mean aortic pressure and cardiac output) (table I). This effect was also accompanied by a smaller decrease in coronary blood flow. Similarly, myocardial oxygen consumption was unaffected by MAC concentrations of isoflurane, compared with halothane (table I). The effects on metabolism were more complex, but halothane also depressed glycolysis to a greater extent than did isoflurane. On analysis of the results, it appears that there is no qualitative difference between the effects of the anaesthetics on glycolysis in the working rat heart, but rather that the effects depend on the functional effects, particularly oxygen consumption. At equivalent myocardial oxygen consumptions, the effects of isoflurane and halothane appear to be similar. Thus although these experiments demonstrate that halothane produces more functional depression of the isolated working rat heart than does isoflurane at equi-anaesthetic concentrations, the mechanism of this difference does not appear to be related to the effect on glucose metabolism.

SUMMARY

The major advantage of the isolated heart over isolated cardiac muscle for studying the effect of anaesthetics relates to the maintenance of the anatomy and function of the heart as a pump and the use of the native coronary circulation for cardiac nutrition and oxygenation. For the latter function, perhaps the blood perfused heart-lung preparation is more physiological but less controllable, particularly for metabolic studies. However, both preparations are predominantly useful for evaluating mechanisms and comparative biochemical pharmacology, rather than being relevant for clinical management.

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USE OF CARDIOPULMONARY BYPASS IN STUDIES OF THE CIRCULATION

J. H. LEVY AND C. C. HUG JR

Cardiopulmonary bypass (CPB) provides an important clinical setting to study a complex set of physiological responses to a relatively abnormal state in man. Although CPB from many perspectives represents a controlled form of shock, it nonetheless represents a unique opportunity to study specific human physiological responses to conditions that include constant systemic blood flow, acute haemodilution, hypothermia, exclusion of the lungs from the circulation, regional blood flow abnormalities and protein changes [7]. Considerations that make CPB a useful experimental model to study the effects of anaesthetics on myocardial function will be discussed separately.

CONSTANT FLOW

During CPB, patients receive a continuous flow via a roller pump to provide a specific cardiac output. Arterial pressure changes produced by drugs during constant flow CPB reflect changes in systemic vascular resistance [3, 4]. CPB presents a unique opportunity to study the effects of drugs on the peripheral vasculature as well as their ability independently to affect venous capacitance and arterial resistance vessels. Studies of drug effects on vascular resistance in normal (intact) man can be complex and difficult to interpret, since many drugs exhibit diverse effects on both myocardial function and the systemic vasculature. Morphine, for example, may directly dilate the venous capacitance bed producing decreased preload, release histamine from cutaneous mast cells producing arterial and venodilatation, slow

heart rate, and decrease sympathetic tone [10, 15]. The net effects of the administration of morphine on systemic vascular resistance and myocardial function can be unpredictable, depending upon the blood volume, sympathetic tone and ventricular function (fig. 1). For example, studies evaluating the effects of histamine release by opioids as a significant mechanism for hypotension are open to question [6]. In addition, the effects of antihistamine (diphenhydramine or cimetidine) pretreatment, in producing H_1 - and H_2 -receptor blockade to attenuate hypotension, have been questioned because these drugs alone may increase heart rate and arterial pressure. Patients undergoing CPB with constant blood flow provide an important experimental model in man to resolve questions concerning the effects of drugs on systemic vascular resistance. Although blood is shunted from the lungs and reduced renal and hepatic blood flow occur during CPB, stable conditions can be achieved and the effects of drugs on the peripheral vasculature determined in man. Few studies have been performed using this model. Existing data suggest both fresh frozen plasma and 5% plasma protein fraction are vasodilators (fig. 2) [3, 4].

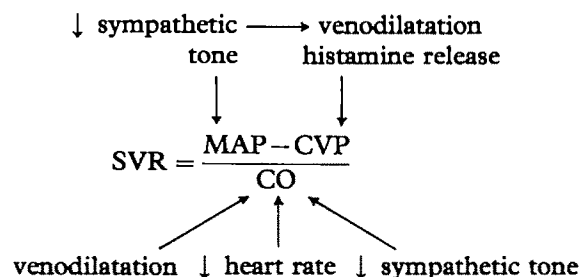


FIG. 1. Effects of a drug, such as morphine, on calculated systemic vascular resistance (SVR) are complex and depend on multiple factors that vary from patient to patient. MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output.

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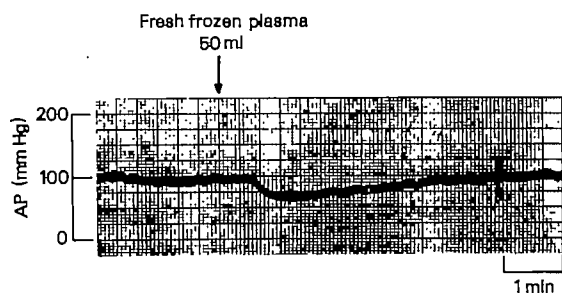


FIG. 2. Effects of fresh frozen plasma 50 ml when administered at constant flow CPB. The decrease in arterial pressure represents a decrease in systemic vascular resistance at constant flow [4] (Reproduced with permission of author and publisher.)

HAEMODILUTION

Patients undergo rapid haemodilution during the initiation of CPB. A colloid or crystalloid priming solution (or a mixture) is used in the CPB circuit to reduce red blood cell concentration. The net effect is to decrease the blood viscosity rapidly; however, other changes occur, including a 40–50% dilution of plasma as well as a decrease in total drug concentrations [7]. The net effect may be a new set of equilibria developing between the concentrations of free and bound drug in plasma and in tissues. The concentration of protein-bound drug may decrease in proportion to the degree of haemodilution, while the concentration of the free drug, which is the pharmacologically active drug form, may remain virtually unchanged or may decrease slightly and transiently following rapid haemodilution [8]. At present very few studies have evaluated changes in free drug concentration during CPB. As the total drug concentration decreases with haemodilution, the apparent volume of distribution increases proportionately, but the free drug distribution volume may not change, or may change to a lesser degree. Although most anaesthetists administer additional doses of drugs at the initiation of CPB based on demonstrated decreases in total drug concentration this may, in fact, be unnecessary, because free drug concentrations may be unchanged or only slightly decreased. The acute effects of haemodilution and the resulting changes in drug concentrations, plasma protein binding, extravascular protein binding, pH and temperature changes, as well as changes in plasma oncotic pressure may produce major intercompartmental movements of fluids and drugs [7]. This would provide a unique clinical setting to evaluate the variables affecting pharmacokinetics more or less independently.

HYPOTHERMIA

Various degrees of hypothermia (20–32 °C) may be used during CPB. Hypothermia will decrease metabolic activity and oxygen requirements, alter regional blood flow, decrease enzymatic function and decrease drug metabolism [7]. In addition, hypothermia will produce slowing of the electroencephalogram and potentiate the effects of anaesthetics and other drugs that depress the central nervous system. Decreased metabolism and elimination of drugs may result in more intense and persistent drug effects, during and after CPB. The effects of drugs on systemic vascular resistance may be altered by changes in temperature. Very few studies have focused on the effects of hypothermic conditions on drug effects and drug disposition.

EXCLUSION OF LUNGS FROM THE CIRCULATION

Total cardiopulmonary bypass effectively excludes the lungs from the circulation, by draining venous blood from the inferior and superior venae cavae directly into the oxygenator and returning it to the aorta by the roller pump. This system abolishes the circulation of venous blood to the lungs, but the flow of arterial blood through the bronchial circulation continues to supply the lung's metabolic needs. Increased blood flow through bronchial and other collateral circulations is often scavenged by a vent placed into the pulmonary vein or into the left ventricle to avoid ventricular distention. Although we consider the lung an organ important for gas exchange, it is a metabolically active organ capable of extensive removal and subsequent enzymatic degradation of endogenous mediators and drugs by endothelial cells. Prostaglandins of the E and F series, 5-hydroxytryptamine, and noradrenaline are rapidly and extensively extracted from blood during their first pass through normal lungs [2, 12]. CPB alters the ability of the pulmonary circulation to clear vasoactive amines and may ultimately modify vasoregulation of the peripheral circulation [12]. This may explain why some patients are so vasodilated, with a low systemic vascular resistance after CPB. The lung is also capable of sequestering drugs such as opioids [1] and propranolol [13]. Washout of substances accumulated in lung may occur as perfusion through the pulmonary vasculature is restored during the initial separation from CPB; drug concentrations may increase in the circulating blood [1, 13].

REGIONAL BLOOD FLOW ABNORMALITIES

Systemic blood flow during CPB in man is usually non-pulsatile, with flow rates ranging from less than to greater than a normal cardiac index. Hypothermia, often utilized for protection of the isolated organ, together with altered perfusion may profoundly modify blood flow distribution to important organs such as the liver and kidneys. Components of the CPB circuit such as the oxygenator and arterial filter are capable of binding both plasma proteins and drugs (e.g. nitroglycerin and fentanyl) [5, 9, 11, 13, 14]. The net effect on drug concentrations in blood can be expected to be quite variable, depending on the pharmacokinetic characteristics of the drug as well as the physiological changes produced by CPB.

PROTEIN CHANGES

Institution of CPB decreases plasma protein concentrations to affect pharmacokinetics as noted above, but it may also produce significant decreases in other plasma proteins important to normal immune processes. After open heart surgery, patients demonstrate decreased lymphocytic responses to phytohaemagglutinin, concanavalin A, pokeweed mitogens and mixed lymphocyte cultures—indices of depressed immune function [16]. The significance of these changes is unclear. However, the circumstances of CPB provide a unique opportunity to study the effects of immunodeficiency states in man.

SUMMARY

In summary, CPB provides a complex set of physiological circumstances during which the patient is subjected to severe physiological alterations with surprisingly few adverse sequelae. Our ultimate goal in performing medical research is to provide scientific insights that improve patient care. Results of studies of animal models may not always be applicable to man. Although CPB possesses faults inherent to any experimental model, it nonetheless provides a unique opportunity to study safely and effectively a variety of physiological and pharmacological variables that affect cardiovascular functions in man.

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THE ACUTE OPEN-CHEST MODEL

H.-J. PRIEBE

The acute open-chest animal model is frequently used to assess the effects of anaesthetics on myocardial function. This model, however, requires interventions which by themselves exert important cardiovascular effects and also alter the cardiovascular responses to subsequent physiological or pharmacological interventions. This must necessarily modify the interpretation of data derived from experiments conducted in this model. Accordingly, for the reader of medical literature and for those planning to conduct experiments in the acute open-chest model, the goals of this short overview are: to discuss the physiological consequences of interventions which are unrelated to the actual study procedure but inherent in this experimental model; to suggest ways to reduce the side effects of these unavoidable interventions; and to provide some reasons why the continued use of this experimental model is justified even at a time when great progress has been made in the use of chronically instrumented animals.

BASIC INTERVENTIONS

There are five interventions which disturb normal physiology in the acute open-chest model: anaesthesia, mechanical ventilation, an open thorax, at times, an open pericardium, and surgical manipulation.

Anaesthesia

It is well known that general anaesthesia exerts a profound influence on cardiovascular control. When compared with the conscious animal, the anaesthetized animal responds very differently to a variety of physiological and pharmacological interventions [5]. The principal physiological differences and differences in response to physiological and pharmacological interventions are

summarized in tables I and II. Most relevant are the differences in baseline autonomic tone, and the reduced myocardial contractility in the anaesthetized animal. In addition, it can be seen that the anaesthetized animal responds very differently to carotid sinus stimulation, and to changes in heart rate (Bowditch phenomenon), in preload (Bainbridge reflex), and in afterload (Anrep reflex).

Similar differences between the anaesthetized and the conscious animal have been observed in response to pharmacological interventions (table II). These data would suggest that the state of anaesthesia *per se* will substantially modify the cardiovascular response to drugs which themselves have an effect on preload, afterload, contractility, heart rate, and systemic and coronary vascular resistance. However, it remains to be proven that all of these differences are primarily the result of the state of anaesthesia rather than the (inappropriate) choice of baseline anaesthesia. Most of the investigations which seemed to establish the fundamental differences between the anaesthetized and the conscious animal have been carried out under pentobarbitone anaesthesia with baseline heart rates and mean arterial pressures in the range 140–160 beat min⁻¹ and 140 mm Hg, respectively. This clearly reflects an unphysiologically increased baseline sympathetic tone which must necessarily modify the cardiovascular response to any subsequent physiological or pharmacological intervention. It has long been felt that “barbiturates render a preparation pathologic rather than physiologic” [3], and only recently has it been shown that pentobarbitone induces an acute cardiomyopathy [1]. This is also suggested by the combination of increased sympathetic tone and reduced baseline myocardial contractility (table I). There is, in fact, mounting evidence that it is not necessarily the state of anaesthesia *per se* that is primarily responsible for the differences between the anaesthetized and the conscious animal, but rather the kind of basal anaesthesia [1]. The appro-

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TABLE I. *Physiological differences and differences in response to physiological interventions between anaesthetized and conscious animals. SVR = Systemic vascular resistance; CVR = coronary vascular resistance. + = Present; (+) = of questionable physiological relevance; - = not present*

	Anaesthetized	Conscious
Predominant autonomic tone	Sympathetic	Parasympathetic
Basal myocardial contractility	Reduced	"Normal"
Effect of carotid sinus reflex on		
Contractility	+	(+)
SVR	(+)	+
Heart rate	(+)	+
CVR	(+)	+
Bowditch phenomenon	+	-
Bainbridge reflex	-	+
Anrep reflex	+	-

TABLE II. *Differences in response to pharmacological interventions between anaesthetized and conscious animals. ↑↑ = Markedly increased; ↑ = increased; (↑) = questionable increase; - = no change; ↓ = decreased*

	Anaesthetized	Conscious
Contractility		
Noradrenaline	↑↑	↑
Dobutamine	↑↑	↑
Dopamine	↑↑	↑
Digitalis	↑	-(↑)
Cardiac size		
Noradrenaline	↓	-
Dobutamine	↓	-
Heart rate		
Noradrenaline	↑	↓
Coronary vascular resistance:		
Noradrenaline	↓	↑
Dopamine	↓	↑
Digitalis	-	↑
Morphine	↓	↑

TABLE III. *Suggestions for basal anaesthesia*

1. Consider the use of premedication
2. Select anaesthetics with minimal cardiovascular side effects
3. Use only continuous infusions of i.v. drugs
4. Consider the use of a combination of drugs
5. Test for preservation of baroreceptor activity
6. Aim at physiological basal heart rate and arterial pressure

priateness of using pentobarbitone as the basal anaesthetic in cardiovascular investigations must, therefore, seriously be questioned.

An alternative approach to a baseline anaesthetic is proposed in table III. Use of an effective premedication will result in a quiet animal, and a more physiological basal autonomic tone. In addition, the amount of barbiturate needed for induction of anaesthesia can be reduced considerably, and the pain of the surgical preparation (cut-downs, thoracotomy, sternotomy) is

in part covered by the analgesic drug. By using continuous infusions we can often reduce the total amount of anaesthetics given, and we can certainly avoid big swings in plasma concentrations with subsequent changes in autonomic tone and cardiovascular function. The use of more than one drug increases the likelihood of additional drug interactions. However, since the dose of each individual drug can be reduced considerably, the overall side effects of the basal anaesthesia may also be reduced this way. Before establishing basal anaesthesia, it is worthwhile to test for preserved baroreceptor activity. This may be done by injecting a short acting vasodilator (e.g. nitroglycerin) and observing whether the change in heart rate in response to the decrease in arterial pressure is similar to that which has been described for the conscious animal. Finally, any basal anaesthesia should produce normal heart rates and arterial pressure.

Mechanical ventilation

The consequences of mechanical ventilation with an open thorax are well known. Venous return may decrease secondary to the decrease in venous filling gradient. This will in turn reduce preload, and stroke volume and the developed systolic pressure may subsequently decrease.

If the chosen tidal volumes are too low or too high, pulmonary vascular resistance (an index of right ventricular afterload), P_{aCO_2} , P_{aO_2} , and pH may all be adversely affected.

In order to keep those side effects at a minimum, adequate fluid administration, relatively high tidal volumes (preferably with low positive end-expiratory pressure because of the tendency for airway collapse), and frequent monitoring of arterial blood-gases and pH are mandatory.

Open thorax and pericardium

The acute loss of negative intrathoracic pressure will result in reductions of the venous filling gradient, the cardiac filling pressures and of lung volume. Lung-heart interaction will be reduced. The open thorax is certainly one of the main reasons why these animals tend to become hypothermic very readily.

If, in addition to the thorax, the pericardium is also opened, then cardiac geometry, the degree of ventricular interaction, cardiac distensibility, and cardiac filling pressures will be affected further. However, these effects are probably of some physiological relevance only at higher end-diastolic volumes and pressures [2,6]. Thus if experiments are being performed that are likely to cause significant changes in ventricular volumes and pressures, the pericardium should preferably be kept intact or, at least, re-closed after surgical preparation.

Obviously, some of the changes following the opening of the thorax and pericardium are similar to those following the institution of mechanical ventilation. Preload tends to decrease, which tends to reduce stroke volume and developed systolic pressure. The lungs tend to collapse and this may affect pulmonary vascular resistance and arterial blood-gas tensions. There is also the risk of hypothermia developing so, again, adequate volume replacement, adequate tidal volumes (preferably with low PEEP), and monitoring of body temperature are essential.

Surgery

The potentially adverse effects of acute surgical manipulation consist of increased sympathetic tone as a result of inadequate analgesia, hypovolaemia as a result of inadequate fluid replacement, and trauma to myocardium, coronary vascular endothelium or coronary artery innervation following placement of measuring devices (e.g. piezoelectric crystals, electromagnetic flow probes). As mentioned earlier, increased sympathetic tone will induce a variety of neuro-humoral changes which are likely to modify the cardiovascular response to subsequent interventions. Effective premedication or transient deepening of the level of anaesthesia will help to blunt the increase in sympathetic tone.

Trauma can only be kept to a minimum if the preparation is performed by a technically very skilled person. An excessively traumatic preparation or unphysiological baseline signals must not be accepted for subsequent data analysis. The trauma of recent surgery may modify the effects of subsequent interventions [4].

MONITORING

The acute open-chest model carries the potential for many adverse effects which may significantly modify the results independently of the actual study programme. Whenever using this model it is, therefore, imperative to provide a minimum of additional information which allows some estimation of the animal's general homeostasis. Only on such background information is it possible to judge the physiological and clinical significance of data obtained in the acute open-chest model.

Most of the parameters listed in table IV reflect ventilatory and fluid management. Thus the more complicated and potentially more traumatic the preparation becomes, and the longer the experiment lasts, the more we need time controls. This

TABLE IV. *Essential information required when using the acute open-chest model*

Mode of ventilation
Fluid regimen
Urine output
Arterial blood-gas tensions/pH
Haematocrit
Body temperature
Time controls

TABLE V. *Reasons for using the acute open-chest model*

-
- | |
|---|
| 1. Model simulates clinical reality |
| 2. Certain study programmes are facilitated by open-chest |
| 3. More simultaneous measurements possible |
| 4. Less sophisticated animal care facilities required |
-

is the only way to exclude spontaneous deterioration of the preparation with time.

WHY USE THE MODEL?

Despite the drawbacks inherent in the acute open-chest model, there are definite advantages (table V)—provided we take the necessary precautions referred to in this overview. One might very well argue that, in reality, we rarely give a single anaesthetic drug to an unpremedicated patient without any form of surgery going on. What we usually do is add an anaesthetic to some basal anaesthesia while some form of surgery is going on. So, why not test the cardiovascular effects of an anaesthetic under conditions which somehow mimic clinical reality? Of course, the information that we will obtain this way will be different from a "pure" pharmacological approach, but it will still have clinical relevance.

The acute open-chest does not pose the problems of postoperative infections, adhesions and uncorrectable malpositioning or malfunctioning of equipment. This, in general, should allow simultaneous registration of more technically satisfactory signals.

Last, but not least, this model requires less

sophisticated animal care facilities compared with those required for chronically instrumented animals. This includes logistic, financial and manpower aspects which may well become the limiting factor. However, I do believe that, if we take the necessary precautions to maintain general homeostasis as well as possible, and if we are aware of the limitations of this model, the use of the acute open-chest model will continue to contribute valuable information on the effects of anaesthetics on myocardial function.

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ACUTE CLOSED-CHEST CANINE MODEL FOR ANAESTHESIA RESEARCH

P. A. KAPUR

The choice of a particular model for investigative work is determined by a number of factors, including the interests and background of the investigators, the research hypotheses being tested, as well as the resources available in the laboratory and those available in the institution of which it is a part. In this review of a closed-chest model used in the cardiopulmonary research laboratory of the Department of Anesthesiology at the University of California, Los Angeles, I will discuss the points in favour of such a model, its limitations, the types of instrumentation possible with a closed-chest preparation, aspects of the technique as practised, and actual data obtained with this model.

First, why choose a closed-chest model for cardiovascular research? After all, with a closed-chest preparation, one has to approach the heart from the periphery, without direct access to the organ and tissues one is studying. As can be seen in table I, there are a number of reasons why such a model may be chosen. First, it is closer than many other models to the clinical situation, since the subjects are intact with functioning neural and humoral influences. Second, there are minimal perturbations of the intact subject by the methods used, notably, an absence of surgical stress and the attendant physiological alterations of an open chest, that may result in neural interruptions, hormonal alterations, fluid shifts, temperature differentials, dessication of organ surfaces, tissue disruption, and so on. Merin [14] has recently summarized available work on the interactions of calcium channel blocking drugs during anaesthesia, and came to the conclusion that the effects of such drugs were indeed different in the intact subject compared with the effects observed in open-chest preparations. In comparison with

chronically instrumented preparations, the acute closed-chest model is not exposed to chronic catheters as sources of infection, clot, adhesions and the like. Investigations using chronically instrumented animals may not be able to report a full set of data points for the different parameters measured because of malfunction or other difficulties associated with chronic catheters [1, 15, 17]. In some types of experiment this could possibly lead to misinterpretation of results as some animals are represented for one variable and not for another.

As a result of minimal perturbations, not only of the physiology of the subject, but also to the anatomy, by a closed-chest preparation, frequently the animal subject may be allowed to recover after an experiment, if suitable limitations to the procedure have been observed. The animal can therefore serve as its own control for subsequent aspects of a study. This not only mimics the clinical situation, where patients recover after an anaesthetic, but also contributes to the conservation of animal resources and serves to emphasize meticulous and humane treatment of animal subjects. Variability of experimental results may be reduced by utilizing the same subjects as their own controls.

In addition, and not to be taken lightly, is the fact that the use of acute closed-chest preparations minimizes the animal maintenance procedures

TABLE I. *Advantages of an acute closed-chest animal model for anaesthesia research*

Similar to the clinical situation.
Minimal perturbation of the intact subject by the method:
Absence of surgical stress.
Absence of physiological alterations of an open chest.
No chronic catheters as sources of infection, clot, adhesions, etc.
Conservation of animal resources.
Minimized animal maintenance.

required when compared with a chronically instrumented preparation. The latter requires exceptional animal quarters in order to maintain patency and asepsis of the catheters. Furthermore, personnel must be available every day of the week to flush the catheters several times daily with heparinized saline solution. Many centres have neither ideal settings nor sufficient personnel for continuous care of chronically instrumented animals. An acute model then is an alternative.

Accepting that one has chosen an acute closed-chest model for study, one must recognize the limitations of the model and choose appropriate research hypotheses for testing. An obvious limitation is that methods must not require a thoracotomy or laparotomy. Thus much of the data will be collected from catheters placed by way of peripherally accessible vessels, with their attendant limitations. The availability of fluoroscopy can be extremely helpful at times, for example for the placement of a coronary sinus catheter. Nuclear methods for evaluating aspects of cardiac function or the presence of myocardial ischaemia are increasingly becoming available as productive collaborations develop between nuclear radiologists and anaesthesia investigators. Echocardiography and colour Doppler techniques are also relatively new additions to the investigative armamentarium which can be fairly simply applied to a closed-chest preparation.

Awake controls are possible with many of the measurement techniques used with closed-chest preparations. The animals are trained in advance to lie still in the laboratory setting. On the day of the experiment any required catheters are inserted after infiltration of the site with local anaesthetics. In contrast, if baseline anaesthesia is administered before obtaining the control data, one cannot test any hypothesis that depends upon a comparison between the awake and the anaesthetized state. However, many questions are suitable for an anaesthetized preparation. A few of many examples include: effects of varying anaesthetic concentrations on a particular condition; comparisons of different anaesthetics under the circumstances being studied; effect of any other condition or drug superimposed upon the anaesthetic state; hormonal responses to pharmacological or physiological manoeuvres during anaesthesia and alterations thereof.

Studies undertaken at the cardiopulmonary research laboratory of the Department of Anesthesiology at the UCLA School of Medicine, have

been related to various aspects of the cardiovascular interactions of newer cardioactive drugs with anaesthetics. These have included: arrhythmia studies with verapamil [6, 7], comparison of the influence of the different inhalation anaesthetics upon verapamil pharmacodynamics [3], pharmacodynamic studies of diltiazem with varying anaesthetics [4, 5], interactions of beta-adrenergic blockers with verapamil comparing barbiturate with halothane anaesthesia [8, 18], a series of studies related to the properties of the newer cardiotonic drug amrinone [11–13], and continuing studies of the cardiovascular relationships between local anaesthetic compounds and calcium channel blocking drugs.

In considering the use of the same animal for repeat studies, several important points must be kept in mind. First, it is wise to use conditioned animals for this purpose. Conditioned animals have been under observation for signs of disease, infection or pregnancy for a period of time and have received the appropriate prophylactic immunizations, deworming procedures if indicated, dipping in disinfectant solutions for elimination of external parasites, and so on. In this manner, the contribution to the experimental results of such conditions will be minimized. If the animal is to be allowed to recover between experiments, aseptic techniques should be utilized for catheter placement, parenteral solutions, i.v. tubing, etc. Provision should be made for follow-up antibiotic therapy, catheter site checks and periodic health examinations. The author's laboratory regularly follows and charts the animal's weight and haematocrit. Any animal that does not maintain its weight at or above the initial value or its haematocrit above 30% is withdrawn from further study. Dietary supplements to the standard vivarium fare and oral iron solutions may be given to maintain the animals in good health. To reduce the incidence of a low haematocrit, the amount of blood sampling per experiment is limited consistent with the study data to be obtained. On occasions, if a procedure required a larger number of blood samples, cross-matched donor dog blood has been given to replace the losses. In addition, for survival studies, the experimental procedures are immediately abandoned in the event of hypotension (mean arterial pressure < 50 mm Hg), arrhythmia, etc. The pharmacological effects of the drug under study are antagonized and the animal allowed to recover.

It is also important, in reporting results from an

intact preparation, that the investigators note the details of the anaesthetic technique, the ventilatory parameters, the acid-base status of the animal, the body temperature at the time of study, and blood chemistry or haematocrit values if the latter are available, so that the reader of the work may determine that the physiology was indeed being "minimally perturbed" by the technique.

An additional, but by no means mandatory, aspect of the model being discussed is the presence of a chronic tracheostomy. The technique [16] results in the skin-covered sternohyoid muscle covering the permanent tracheostomy when this is not in use. At the time of an investigation, a tracheostomy tube is inserted after topical application of a small amount of local anaesthetic spray to the trachea. The tracheostomy allows easy access to the trachea, even in an awake animal, for inspired and expired gas sampling and inhalation anaesthetic inductions. Thus the technique eliminates the need for adjuvant sedatives, barbiturates or neuromuscular blocking drugs, or the necessity for a stressful mask induction. Between investigations the tracheostomy tube is removed and the animal uses its upper respiratory tract to provide the normal humidification and filtering of inspired air, thus minimizing the incidence of tracheobronchitis. Animals have been maintained for more than 1 year in good health.

As mentioned, quite a variety of techniques are applicable to the acute closed-chest model (table II). Inspired and expired gas sampling can be used to determine oxygen consumption and carbon dioxide production, as well as to regulate anaesthetic depth (end-tidal concentrations). Arterial access for measurement of pressures and blood sampling is possible percutaneously by way of the femoral artery to the aorta. In addition, a carotid artery loop may be located superficially for chronic needle sampling or, alternatively, a very careful small cutdown to reach the carotid artery can then be closed at the end of the procedure. Other major vessels that arise from the aorta are accessible from the femoral vessels using fluoroscopic control. Venous access for measurement of pressures, blood sampling, or drug administration is available percutaneously by way of the external jugular veins (which are quite large in the dog), yielding access to the superior and inferior vena cavae, the right heart (atrium, ventricle), pulmonary arteries (pressures, thermodilution cardiac output), and the coronary sinus (pressures,

TABLE II. *Investigative techniques possible using an acute closed-chest animal model for cardiovascular research*

Inspired and expired gas sampling
Arterial access and blood sampling
Via femoral artery to aorta
Carotid artery
Other major vessels off the aorta accessible under fluoroscopic control
Venous access and blood sampling
External jugular vein
Superior and inferior vena cavae
Right heart
Right atrium and ventricle
Pulmonary artery: cardiac output, mixed venous samples
Coronary sinus
Femoral vein
Peripheral veins
Electrophysiology
Surface, oesophageal electrocardiograms
Specialized catheters for intracardiac recording (bundle of His, etc.)
Pacing catheters
Left heart catheterization
Chamber pressures
Fluid-filled catheters
Micromanometer-tipped catheters
Fibreoptic catheters
Left ventricular dP/dt
Ejection fraction
Rapid-response thermistor-tipped catheter
Angiographic methods
Nuclear methods
Ventricular volumes
Echocardiographic estimation
Impedance catheter
Rapid-response thermistor-tipped catheter
Other
Thallium scanning
Coronary artery catheterization
Endocardial biopsy
Postmortem required
Regional blood flows by microsphere techniques
Gross and microscopic tissue examinations

coronary blood flow, myocardial oxygen consumption, myocardial drug and metabolite extraction); the femoral veins; or peripheral extremity veins.

In the closed-chest model various electrophysiological measurements may also be made. Surface or oesophageal electrocardiograms can be obtained. Specialized catheters may be placed by

way of percutaneous introducers to the right heart for intracardiac recording (bundle of His, etc.). Transvenous pacing catheters may also be used. Left heart catheterization may be achieved from the femoral artery for measurement of pressures by using a fluid-filled catheter, a micromanometer-tipped catheter, or one of the newer fiberoptic catheters, and left ventricular dP/dt may be differentiated therefrom. Cardiac ejection fractions may be estimated by a rapid-response thermistor-tipped catheter [9], by angiographic methods, or by nuclear methods. Ventricular volumes may be estimated in the closed-chest subject by use of echocardiographic techniques, a catheter that senses changes in electrical impedance in the blood in the ventricle chamber [10] or from the rapid-response thermistor-tipped catheter.

Other techniques of interest to cardiovascular investigators that are possible in the closed-chest animal include thallium scanning to evaluate areas of myocardial ischaemia, nuclear magnetic resonance and positron emission scanning for changes in the metabolism and biochemistry of the heart, coronary artery catheterization, and endocardial biopsy using the transvenous technique. If the animal is not needed for subsequent investigations, then regional blood flows by microsphere techniques and pathological examination of tissues are also possible.

Regardless of the techniques chosen, recognition of the limitations of the data obtained and rigorous attention to the details of the technique are necessary. For the sake of discussion we will consider the thermodilution coronary sinus catheter technique as advanced by Ganz and colleagues [2]. The coronary sinus catheter can be used only to measure global left ventricular function. Although newer versions now have a second orifice to determine great cardiac vein blood flow, specific information about multiple zones of the ventricle cannot be obtained with this technique. In addition, proper location of the catheter tip is essential. The proper location can be confirmed by use of fluoroscopy with small injections of dilute dye solutions and observation of the proper coronary sinus wave form and PO_2 . When doubts occur, cold saline can be injected to the right atrium while checking the thermistor temperature of the catheter. Since any of these manoeuvres may transiently affect haemodynamics, they must be performed with several minutes separation from data collection times.

There must also be uniform mixing and delivery of the thermal indicator. Precautions in this regard include continuous infusion for at least 1 min before measurement, transient cessation of ventilation, recording the temperature curves, and taking all measurements in duplicate. Thus the critical evaluation of a research report that incorporates this technique depends upon the inclusion by the investigators of as much information as possible about how the limitations of the technique in question were minimized and what assumptions have been made in interpreting the results.

SUMMARY

An acute closed-chest canine model may be useful to study a wide variety of hypotheses relevant to cardiovascular physiology and pharmacology in circumstances which are clinically relevant. The absence of anatomical perturbations allows recovery of the subjects for conservation of animal resources and to serve as their own controls. The use of a chronic tracheostomy has facilitated inhalation anaesthesia without the use of other agents and allows easy access to the trachea in awake animals with minimal adverse effects. A thorough understanding of the techniques utilized aids in the interpretation of results obtained with this as with any other model.

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CHRONIC INSTRUMENTATION TECHNIQUES FOR HAEMODYNAMIC MEASUREMENTS

M. ZIMPFER

Most of the knowledge of cardiovascular physiology and pharmacology is based on experiments which have been conducted on animals in the anaesthetized state, often with an open chest, and the tacit assumption that general anaesthesia does not modify the conclusions derived from these experiments to a major extent. However, research in *chronically instrumented* experimental animals has shown that the methodological requirement for basal anaesthesia—that is, the impact of anaesthetic drugs in the absence of the particular anaesthetic under study—may cause a considerable disruption of the autonomic control of the cardiovascular system [1, 2, 4, 7, 12, 15, 16], a profound shift in baseline haemodynamics [1, 2, 4, 7, 10–16], and myocardial function and coronary haemodynamics [1, 3, 10–14, 16], variables which are of fundamental importance in studying the impact of various anaesthetics on the cardiovascular system. It is, therefore, important to conduct sequential haemodynamic measurements enabling comparisons of the conscious *v.* the anaesthetized states. The goal of the present article is to present some of the chronic instrumentation techniques for study of the effects of anaesthetic agents on overall haemodynamics, coronary blood flow and regional myocardial function in comparison with the conscious state.

METHODS

Implantation of instrumentation is carried out in trained, premedicated animals using general anaesthesia with either pentobarbitone 25–30 mg kg⁻¹ i.v. or a volatile anaesthetic after induction of

anaesthesia with thiopentone, and strict aseptic surgical techniques. The catheters and transducer wires are exteriorized in the lateral chest wall, tunnelled subcutaneously to positions between the scapulae, and protected by fitting the dogs in a jacket of stocking gauze. The animals are placed on a 3-day postsurgical regimen of antibiotics. Two to 4 weeks are allowed for recovery from the effects of surgery. Experiments are then conducted for several subsequent weeks and at least 3 days apart to eliminate residual effects of pharmacological agents. It is mandatory that none of the animals has an arrhythmia or systemic infection and that all can exercise normally. While the conscious unsedated dogs recline quietly, continuous measurements of various haemodynamic parameters under various experimental conditions, for example in the presence or absence of other pharmacological agents or under the influence of physiological perturbations, can be obtained for later paired comparisons with anaesthetized states or with other experimental models, for example after isolation of the hearts and lungs from the systemic circulation [3, 15]. For subsequent analysis the data can be recorded on a direct writing oscillograph and collected on a multi-channel magnetic tape recorder.

Measurements of aortic flow and aortic pressure (fig. 1)

Through a left thoracotomy in the 4th intercostal space, electromagnetic flow transducers (Zepeda Instruments or Gould Instruments) are implanted around the ascending aorta and heparin-filled Tygon catheters are implanted in the ascending aorta. Arterial pressure is measured using the catheter and a strain gauge manometer (Statham Instruments). Square-wave electromagnetic flowmeters (Benton Instruments or Gould Instruments) are used to measure cardiac output. Zero aortic blood flow is assumed to occur during mid- and late-diastole. Flow probes are

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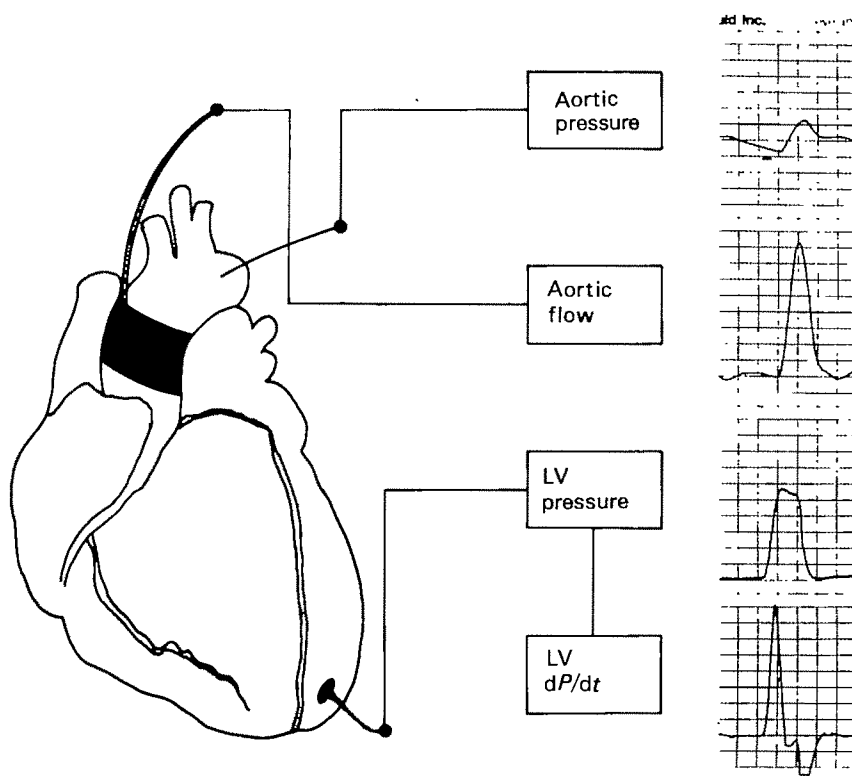


FIG. 1. Measurement of aortic flow and aortic pressure.

calibrated *in vitro* with a gravity flow system. It is noteworthy that, in contrast to what is possible with acute experiments, reliable measurements of aortic flow can be obtained over a wide physiological range, in particular even at very low systemic pressures, as the flow probes are firmly adherent to the ascending aorta by the time the experiments are performed.

Measurements of left ventricular pressure and internal left ventricular dimensions to study global left ventricular performance (fig. 2)

Via a thoracotomy through the left 5th intercostal space, miniature left ventricular pressure gauges (Konigsberg) are inserted to the left ventricular cavity through an apical stab wound. The gauges are calibrated against a mercury manometer *in vitro* before implantation and after their recovery from the animals. The left ventricular pressure gauges can also be cross-calibrated *in vivo* against measurements of aortic or left atrial pressures. Ultrasonic diameter-transducers are placed on opposing endocardial surfaces through small stab wounds in the anterior and posterior

walls of the left ventricle to measure internal minor axis diameter. An improved ultrasonic transit time dimension gauge [5,6] is used to measure the distance between various pairs of ultrasonic transducers. This instrument generates a voltage linearly proportional to the transit time of acoustic impulses travelling at the sonic velocity of approximately $1.5 \times 10^6 \text{ mm s}^{-1}$ between the 3-MHz piezoelectric crystals, thus giving a record of instantaneous internal left ventricular diameter. At a constant room temperature, the thermal drift of the instrument is minimal, that is less than 0.01 mm in 6 h. The frequency response is flat to 50 Hz. Any drift in the measuring system (that is, the instrument electronics), the data tape recorder, and the oscillograph that displays data, is eliminated by periodic calibrations. This involves substitution of pulses of precisely known duration from a crystal-controlled pulse generator with a basic stability of 0.001%. Any major change in crystal alignment can be detected in the received signal and invalidates the experiment. The position of the miniature ultrasonic transducers is confirmed at postmortem and minimal

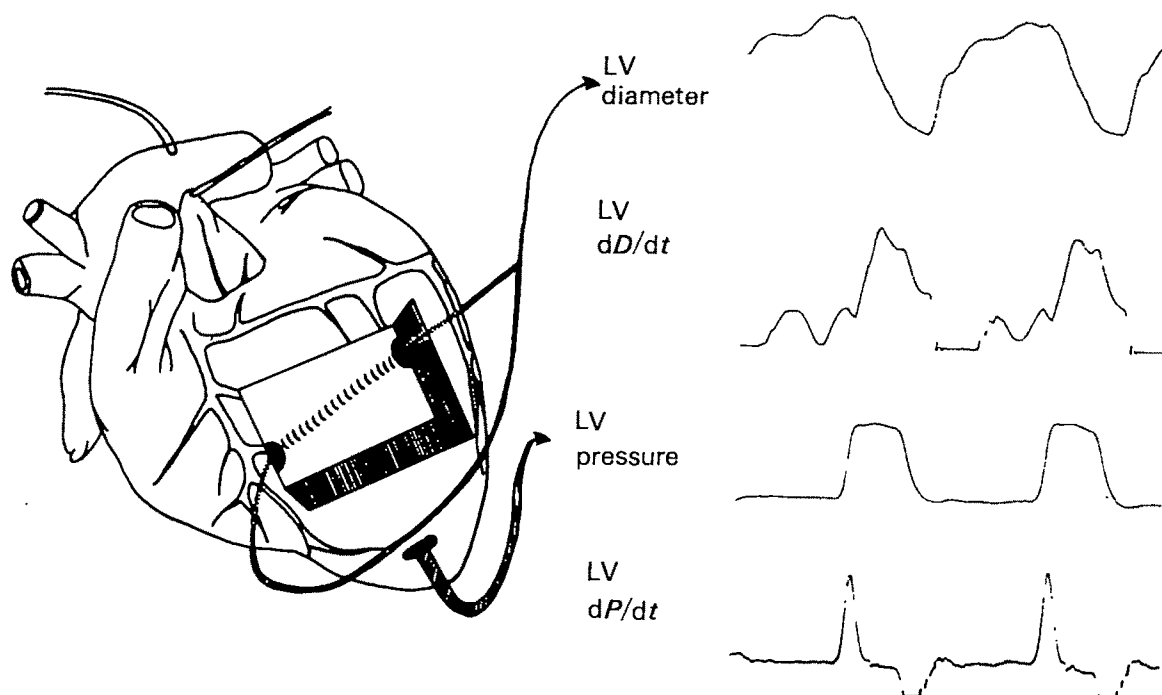


Fig. 2. Measurement of left ventricular pressure and internal left ventricular dimensions to study global left ventricular function.

fibrosis extending < 1 mm from the transducer can be observed at the site of implantation. Parameters derived from the pressure and diameter signals include left ventricular $dP/dt_{\max}$ and left ventricular $dD/dt_{\max}$ (the velocity of myocardial fibre shortening), using analogue operational amplifiers. Expanded left ventricular pressure is used to determine left ventricular end-diastolic pressure.

Measurements of coronary blood flow and the regional contractile function of both normal and chronically ischaemic myocardium (fig. 3)

Doppler ultrasonic flow transducers and hydraulic cuff occluders are placed around the circumflex coronary arteries, a few millimetres below the edge of the left atrial appendage. A ligature is passed beneath the freed coronary artery, just distal to the flow transducers, and tied around the vessel, with a 20-gauge needle along its side. The needle is then immediately withdrawn, thus allowing some flow through the coronary artery. At the time of the experiments, either absence of reactive hyperaemia after a 20-beat coronary occlusion is found or the circumflex

coronary artery is gradually further constricted by inflating the hydraulic occluder until exhaustion of the vasodilator response occurs. Following abrupt longer occlusions of the coronary artery, a progressive further reduction in the extent of muscle shortening occurs until there is paradoxical systolic lengthening which persists at least as long as the occlusion is maintained. Pairs of ultrasonic transducers are placed subendocardially, parallel to the muscle fibres in normal and ischaemic zones. These transducers measure distances between the different pairs of crystals. If, at postmortem, the transducers are not found to be in the endocardial third of the left ventricular wall, the data are discarded.

End-diastolic segment length is defined at the beginning of the sharp upslope of the left ventricular pressure tracing and end-systolic segment length at the time of closure of the aortic valve as indicated by the dicrotic notch on the aortic pressure tracing. The following formulae are used for the derivation of segment lengths:

Segment shortening (SS) (ΔL) = EDSL - ESSL

where EDSL = end-diastolic segment length; ESSL = end-systolic segment length.

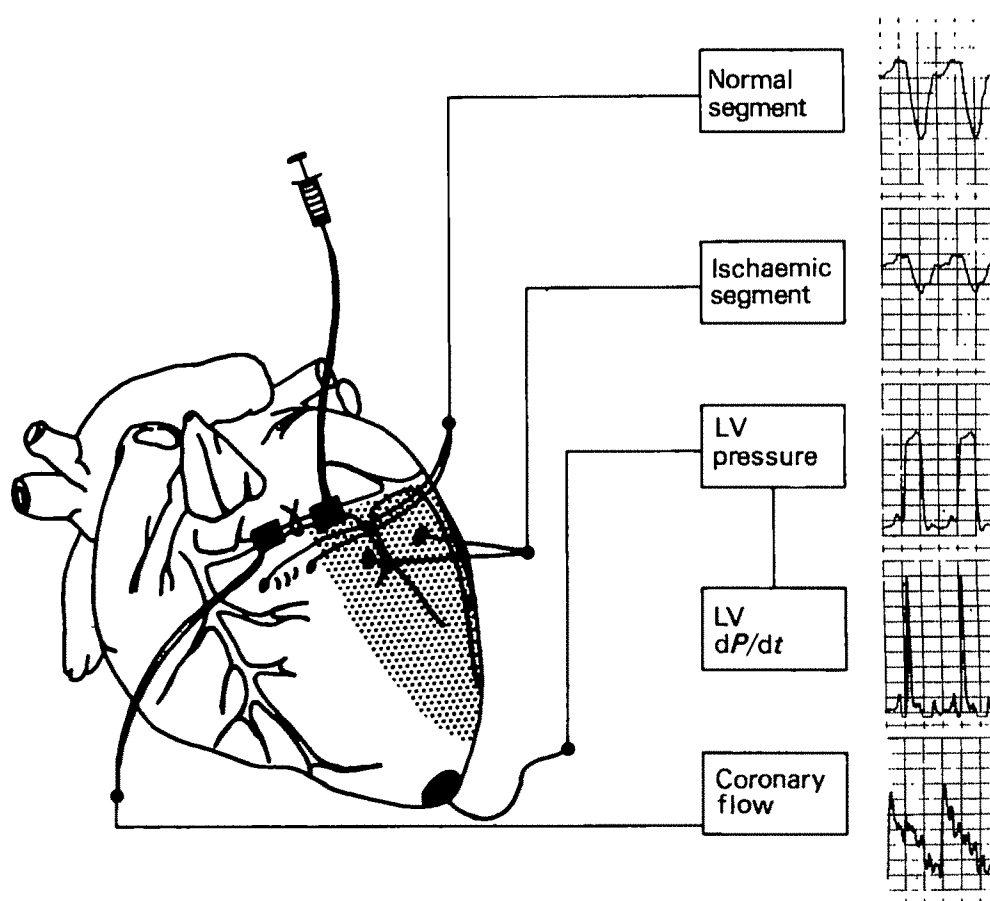


FIG. 3. Measurement of coronary blood flow and the regional contractile function of both normal and chronically ischaemic myocardium.

$$\text{Per cent shortening (SS \%)} = \frac{(\text{EDSL} - \text{ESSL})}{\text{EDSL}} \times 100$$

$$\text{Segment work (SW)} = \text{SS} \times \text{MAP}$$

where MAP = mean arterial pressure.

Left circumflex coronary blood flow is measured with an ultrasonic Doppler flowmeter. This system, which has been described in detail previously [8, 9], has a reliable zero reference. The electrical zero blood flow is determined repeatedly and confirmed by calibration terminally. An adequate signal:noise ratio is established by displaying the flow signal on an oscilloscope and listening to the audio Doppler signal. In the case of inaccuracies resulting from poor acoustical coupling between transducer and blood vessel or an inadequate signal:noise ratio, the recorded

data should not be used. The following formulae are used for calculation of coronary flow:

$$\text{CF} = F_D \times A^2$$

where F_D = Doppler frequency shift;
 A^2 = Cross sectional area of the left circumflex coronary artery.

For coronary conductance:

$$\text{CC} = \text{CF} / \text{MAP}$$

where MAP = mean aortic pressure.

The relationship between velocity, as determined by the Doppler flowmeter, and volume flow in linear as long as the cross sectional area of the blood vessel within the transducer remains constant. This linear relationship between velocity and volume flow has been demonstrated repeatedly and confirmed by timed collections of

blood flow. At the time of postmortem, the vessels are firmly attached to the flow transducers by a fibrous scar which minimizes changes in the cross-sectional area of the vessel within the flow transducers.

CONCLUSIONS

Chronic instrumentation techniques are suitable to evaluate the effects of anaesthesia on: basal cardiac function; responses to changes in cardiac preload, afterload and frequency; the integrative circulatory control such as occurs with stimulation of baroreceptors and chemoreceptors and responses to a wide variety of physiological and pharmacological interventions; and the effects of anaesthesia on chronically diseased myocardium. As anaesthetics can affect almost every aspect of the circulatory system, the importance of conducting experiments in comparison with the intact integrative control of the circulation in the conscious organism should be recognized.

SUMMARY

Research in *chronically instrumented* experimental animals has shown basal anaesthesia may cause a considerable disruption of the autonomic control of the cardiovascular system, and a profound change in basal haemodynamics, myocardial function and coronary haemodynamics—variables which are of fundamental importance in studying the impact of various anaesthetics on the cardiovascular system. It is, therefore, important to make sequential haemodynamic measurements which enable comparisons to be made of the conscious *v.* the anaesthetized state. The present article describes some of the chronic instrumentation techniques used to study the effects of anaesthetic agents on overall haemodynamics, coronary blood flow and regional myocardial function in comparison with the conscious state. It is suggested that the effects of anaesthesia on the integrative control of the circulation are not sufficiently recognized.

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CLINICAL POSSIBILITIES AND LIMITATIONS OF TECHNIQUES ASSESSING THE EFFECTS OF ANAESTHETICS ON MYOCARDIAL FUNCTION

J. TARNOW

From a theoretical point of view this subject could be divided into methods assessing the effects of anaesthetic drugs on left or right ventricular function, on pump function or muscle function, global or regional myocardial function, on systolic and diastolic function, or into invasive or non-invasive techniques.

However, for practical purposes it appears reasonable to give a more general view of the methods applicable to clinical anaesthesia.

ELECTROCARDIOGRAPHY AND DIRECT ARTERIAL PRESSURE MEASUREMENT

The ECG is useful for detecting drug-induced changes in heart rate, arrhythmias, heart block and ischaemia. However, it does not give any helpful information about myocardial function or cardiac output. It is also important to realize that a normal resting ECG does not exclude the presence of myocardial ischaemia. Direct arterial pressure measurement allows continuous observation of the arterial waveform and the displayed values of systolic, diastolic and mean arterial pressure as well as heart rate. Secondary information may be available if the catheter is advanced centrally into an axillary artery or the aorta. Stroke volume and cardiac output may be derived from the area under the systolic ejection portion [37]. Myocardial contractility may be assessed by deriving the rate of aortic pressure change (dP/dt) which is closely related with left ventricular dP/dt [32]. The diastolic downslope of the arterial pressure wave can be processed mathematically as an exponential decay to yield information about the resistance and capacitance of the arterial system before and during anaesthetic inter-

ventions [26]. A simple computer analysis of the arterial waveform can provide on-line continuous monitoring of systemic vascular resistance (SVR). The apparatus that monitors these changes is called an arterial resistometer; it continuously determines the resistance index, which is the pressure at the time of peak dP/dt derived by the peak dP/dt of the pressure curve in the artery [23]. SVR calculated by the arterial resistometer showed an excellent correlation to thermodilution-calculated SVR ($r = 0.97$).

RATE-PRESSURE PRODUCT

The RPP has achieved widespread application as a predictor of myocardial oxygen consumption ($\dot{V}m_{O_2}$). Although a close correlation has been found in awake patients [3], RPP is less reliable or fails to correlate with $\dot{V}m_{O_2}$ under a variety of anaesthetic conditions and does not predict myocardial lactate production [30], probably because the RPP does not incorporate factors such as contractility and ventricular dimensions which are known to exert an important influence on $\dot{V}m_{O_2}$.

PULMONARY ARTERY THERMODILUTION CATHETER

Although measurement of central venous pressure can (if used sensibly) provide useful information on right ventricular preload and function, it is of limited value in assessing left ventricular function [12]. The availability of flow-directed PA-catheters has not only revolutionized perioperative and intensive care medicine, but has also greatly contributed to an improved knowledge of the effects of anaesthetic drugs on cardiovascular function. However, several errors and limitations in the measurement and interpretation of pressure curves, cardiac output, mixed venous oxygen values and derived data such as systemic and

pulmonary vascular resistances have been recognized and require special attention.

Although pulmonary capillary wedge pressure usually reflects left atrial and left ventricular end-diastolic pressure, it may not reflect actual preload. In patients in whom left ventricular compliance is decreased and diastolic relaxation impaired, a normal end-diastolic volume may be accompanied by a high left ventricular filling pressure [1]. PEEP may also increase wedge pressure without increasing end-diastolic volume [15]. Moreover, disparities between *mean* wedge pressure and left ventricular end-diastolic pressure (LVEDP) have been observed. In patients with a stiff left ventricle as a result of hypertrophy or ischaemia, atrial contraction makes a greater contribution to left ventricular filling and may increase LVEDP much higher than *mean* wedge pressure. To avoid underestimations of LVEDP in these patients, the a-wave of the wedged pressure trace—rather than mean wedge pressure—should be measured [11].

Equating wedge pressure with left atrial pressure assumes an open circuit from the catheter tip to the left atrium. This is not the case if the catheter is located in zones I or II of the pulmonary vascular bed, where alveolar pressure is greater than pulmonary arterial or venous pressure. Fortunately, since most of the blood is flowing into zone III, most PA-catheters will also float into this zone. However, when vascular pressures are low or when PEEP increases alveolar pressure, zone III may be converted to zone II. In these cases alveolar pressure may exceed pulmonary venous pressure and wedge pressure will reflect alveolar and not left atrial pressure [33,34].

It is also important to realize how PA-pressures are recorded. Particularly in patients breathing spontaneously, pressures should always be read directly from the screen or strip recorder at end-expiration. Automated digital readouts have the disadvantage that all ventilatory artefacts in patients with wide swings in ventilation are averaged, leading to clinically important errors in wedge and diastolic PA-pressure [7].

Since Swan-Ganz catheters include the ability to measure cardiac output, one should also be familiar with the sources of inaccuracy and unsatisfactory reproducibility of the thermodilution technique. To recognize and avoid pitfalls in the measurement of cardiac output, the temperature curve should always be monitored on a strip-chart recorder.

When mixed venous blood is collected to determine A-V oxygen differences or oxygen consumption, one must realize that contamination of desaturated mixed venous blood by saturated pulmonary capillary blood is possible and may cause an error.

Finally, the use of thermodilution catheters allow calculations of systemic and pulmonary vascular resistances (SVR, PVR) which are frequently used as clinical indices of left and right ventricular afterload. It should be emphasized, however, that systemic vascular resistance may not adequately assess left ventricular afterload since it measures vasomotor tone. This represents only the non-pulsatile component of peripheral load and ignores ventricular internal loading conditions, that is ventricular chamber pressure, dimension and wall thickness. Consequently, SVR may considerably underestimate true left ventricular afterload [20]. In the pulmonary circulation, which is much more distensible than the systemic vasculature, and in which the pulsatile component of flow is so much greater, the mean resistance may only account for 50–60 % of the total impedance to flow, and the use of mean PVR as an estimate of changes in the pulmonary circulation may be quite unjustified [4].

Recently, pulmonary artery catheters with fast-response (50-ms) thermistors have been introduced to allow determinations of right ventricular ejection fraction (RVEF) from diastolic washout plateaux of thermal dilution curves [17]. If right ventricular pressures are also recorded, right ventricular pressure-volume relations can be studied. Although this technique has been validated by radionuclide angiography and echocardiography [16, 17], the conclusions may be erroneous, since the latter methods may not present a "gold standard". Objections to the measurement of RVEF by thermodilution [24] rest on the assumption that adequate ventricular mixing is a prerequisite which is not always obtained. The position of the multi-hole injectate port has to be carefully controlled to ensure optimal indicator mixing. In addition, a normal exponential decay of the thermodilution curve is mandatory; thus measurements of RVEF should not be performed without appropriate recordings of the curve. A varying heart rate or arrhythmias lead to variations in diastolic filling time and may introduce error to measurement of RVEF. Tricuspid regurgitation represents another source of inaccuracy.

ULTRASOUND TECHNIQUES

The application of ultrasonics from precordial, subcostal or suprasternal windows and transoesophageal echocardiography are attractive non-invasive alternatives for pharmacodynamic studies of anaesthetic drugs. While M-mode echocardiography provides useful estimations of left ventricular wall thickness, wall motion and dimensions, and a reasonably accurate assessment of left ventricular volumes over a normal range, its reliability diminishes in large ventricles and those with segmental wall motion abnormalities. Two-dimensional echocardiography has the potential to overcome the problems encountered by the M-mode technique. In reproducing an uninterrupted image of the left ventricular wall in any given projection, the resulting picture provides spatial information, thus allowing a more accurate estimation of volume changes. A high correlation between cineventriculography and two-dimensional echocardiography was found, but LV volumes were systematically underestimated by two-dimensional echocardiography. Despite differences in absolute values, percent changes in ventricular volumes and ejection fraction are comparable with both methods [9].

Two dimensional transoesophageal echocardiography is a relatively new technique and may also be of use as a quantitative research tool to study the effects of anaesthetics on ventricular volumes, but this method can hardly be used in awake patients and has not yet been validated by radiographic or nuclear techniques [19]. Another promising use of echocardiography (preferably from the oesophagus) is the detection of anaesthesia-induced acute abnormalities of regional ventricular contraction which are highly sensitive and relatively specific indicators of myocardial ischaemia. Although the superiority of echocardiography over electrocardiography for the detection of myocardial ischaemia has been demonstrated [29], this technique suffers from the same problem as the ECG, because the signal must be aimed at the ischaemic segment or the changes will be missed.

In addition to its utility in producing images of the moving heart, reflected ultrasound can assess the motion of blood by techniques based on the Doppler shift. At least semiquantitative estimations of cardiac output are possible with a device that combines A-mode aortic root diameter determination and continuous wave Doppler flow

velocity measurement in the ascending aorta. Problems with this technique include varying cross-sectional areas throughout the heart cycle leading to errors in aortic root diameter determination, and the inability to measure aortic root diameter or to obtain acceptable Doppler flow signals in about 10–20% of the patients [35].

In summary, each of the ultrasound techniques discussed has major limitations, the equipment is expensive and usually located in departments of cardiology. This may explain why anaesthetists have been slow to adopt these methods, despite the obvious advantages of non-invasiveness.

VENTRICULOGRAPHY

Although contrast and radionuclide ventriculography are considered to provide the gold standards for measuring volumes and ejection fraction, they are not applicable in the operating room. Not only is the equipment fairly bulky, but the nature of the contrast materials prevents frequent repetition of the measurements. The development of a gamma camera of small size and true mobility which allows semi-invasive bedside pharmacodynamic studies offers obvious advantages [8, 13]. With this computerized nuclear probe (nuclear "stethoscope") a real-time left ventricular time-activity curve can be recorded after *in vivo* labelling of red blood cells with ^{99m}technetium pertechnetate 15–20 mCi, so that LV ejection fraction can be measured beat-to-beat, based upon relative changes in ventricular volumes. Absolute volumes are difficult to obtain with this instrument as a result of the fixed field view of the detector. Further problems include probe positioning over the left ventricle, recording of background activity and radiation safety in the operating room [5].

VENTRICULAR dP/dt

Since changes in the maximum rate of increase in left ventricular pressure (dP/dt_{max}) are known to be highly sensitive to acute changes in contractility, measurement of left ventricular dP/dt may be used to study anaesthetic drugs, provided that high-fidelity catheter-tip manometers are used. Peak dP/dt is largely independent of changes in afterload, but concomitant changes in preload and heart rate can not be disregarded. Because of differences in ventricular mass, further inaccuracy may be induced when comparing peak dP/dt

and other isovolumetric phase indices in different patients [6]. Since left ventricular pressure measurement is highly invasive, this method has been infrequently used to obtain information about the effects of anaesthetics on left ventricular contractility in man.

Maximum dP/dt can not be used to assess right ventricular contractility because the peak pressure increase usually occurs after the opening of the pulmonary valve.

PRESSURE-VOLUME RELATIONSHIP

The contractile state of the ventricle can also be characterized by examining the relationship between the volume of blood remaining in the ventricle at the end of systole and the ventricular pressure at that time. Inotropic interventions have been shown to modify the slope of the end-systolic pressure-volume relationship [14]. The advantages offered by end-systolic pressure-volume analysis are that the relation is preload independent and that afterload is incorporated. In addition, Suga and co-workers [31] have shown that the total ventricular pressure-volume area serves well as a predictor of myocardial oxygen consumption per beat. Because it is difficult to determine ventricular end-systolic pressure and volume in patients, measurements of peak systolic arterial or aortic pressure and echocardiographic volume estimations may be substituted. Alterations in ventricular compliance can be identified by a change in the shape and position of the curve relating left ventricular end-diastolic volume or diameter to left ventricular end-diastolic pressure. Again, these measurements are difficult to obtain and have therefore not been adopted by clinical anaesthesia.

SYSTOLIC TIME INTERVALS

The most widely used method for calculation of systolic time intervals (STI) utilizes a combination of the ECG, a carotid pulse tracing, and a phonocardiogram. From these non-invasively obtained parameters, one can determine the total electromechanical systole (QS_2), the left ventricular ejection time (LVET) and the pre-ejection period (PEP), measured as the difference between QS_2 and LVET. Because the STI vary inversely with heart rate, the primary values must be rate corrected or indexed. A prolongation of PEP, a decrease of LVET, and an increase of the ratio

PEP:LVET indicate a deterioration of myocardial function, provided that preload and afterload are not greatly changed [36]. Since the majority of anaesthetic drugs affect not only inotropy, but also the peripheral circulation, interpretation of the STI is difficult. Although STI are related to the ejection fraction, the scatter of data is too large to warrant the use of STI for predicting left ventricular function as indicated by the ejection fraction [10]. A further drawback is that three separate measurements are required to obtain STI which must be averaged over at least 10 ventilatory cycles to minimize the effect of ventilatory variation.

METHODS OF ASSESSING MYOCARDIAL BLOOD FLOW AND OXYGENATION

To determine the effects of anaesthetics on the coronary circulation is of considerable interest, particularly in patients with ischaemic heart disease. Mean steady state coronary sinus blood flow, myocardial lactate and oxygen extraction as well as derived parameters such as coronary resistance and myocardial oxygen consumption have been measured in response to anaesthesia, mainly by using the continuous thermodilution method [22, 27] or the argon inert gas clearance technique [30]. Both methods estimate average steady-state flow only of the left ventricle and do not record phasic patterns of myocardial perfusion. The development of a coronary sinus thermodilution catheter with two sampling ports and two thermistors allows coronary sinus and regional (great cardiac vein) flow and metabolic determinations [2]. The accuracy and reproducibility of the thermodilution method may be affected by unstable blood temperature as a result of interference from extracardial structures or right atrial blood and malposition of the thermistors against a side branch of the coronary sinus [21]. Limitations of the argon inert gas technique are that only global blood flow and metabolic changes are assessed and that the temporal resolution of the system is relatively low (5–10 min). Both methods are invasive and time consuming. Non-invasive coronary flow studies are possible by using thallium-201 perfusion scans [18] or positron emission tomography [28]. While thallium-201 scans only measure relative perfusion with a limited solution, positron emission tomography (PET) not only allows accurate global and regional flow measurements but, in

addition, provides a qualitative assessment of substrate metabolism in the normal and ischaemic myocardium.

Finally, nuclear magnetic resonance imaging (NMR) is also likely to become a most useful technology for the clinical assessment of blood flow distribution and myocardial biochemistry [25]. Although these methods are not applicable in the operating room, they offer unique possibilities to improve greatly our knowledge of the effects of anaesthetics on myocardial function and oxygenation. Efforts for close scientific co-operation with departments of nuclear medicine are advisable and promise to be highly profitable to our discipline.

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REGIONAL LENGTH AND THICKNESS MEASUREMENTS

E. LOWENSTEIN

For the purposes of this report, I shall define regional length or thickness measurements as the dimensions within one layer of the heart wall, or across the heart wall, respectively. I shall not discuss dimensions across the cavity of the ventricle, compliance changes, and right ventricular length or thickness measurements.

Regional function measurements are used for two distinctly different purposes. The first is to measure function of a region as a representative portion of the entire myocardium. The second, and most common, is to document and quantify inhomogeneous function in different regions of the heart. The most common cause of this appears to be myocardial ischaemia.

Tennant and Wiggers [16] first measured regional ventricular function after occlusion of a coronary artery over 50 years ago. They documented a reproducible series of mechanical events limited to the region supplied by that coronary artery. These changes began within several heart beats, and reached a plateau within several minutes. Restitution of flow was associated with regression of the changes.

The technology they used was cumbersome, and there was little further work until the late 1960s to early 1970s, when sonomicrometry was developed. The epidemic of coronary artery disease (CAD), and recognition of its regional nature stimulated investigative work in this area.

SONOMICROMETRY

Sonomicrometry is now the standard technique for measuring ventricular wall length or thickness. It was used for this purpose in 1969 by Bugge-Asperheim in Kiil's laboratory in Oslo [4] and somewhat later by Dean Franklin in San Diego. The principle is quite straightforward. Pairs of piezo electric crystals are implanted in the heart

wall. Electrical stimulation of one crystal causes it to vibrate, producing an ultrasound signal which travels through heart tissue at the putative speed of sound through water. When it reaches the other member of the crystal pair, the sound activates that crystal, which then generates an electric current. The time from activation of the first crystal (the sender) to activation of the second (the receiver) is proportional to the distance between the crystals. Characteristically, a stimulation repetition rate of 1 Hz is used, yielding a continuous trace of distance between the crystals throughout the cardiac cycle. The crystals vibrate at 3-6 MHz.

This measurement is extremely stable, reproducible and precise over long periods of time. Implantation of crystals in left ventricular myocardium is quite straightforward and easily accomplished. The thin walled right ventricle is more challenging, and far less work has been accomplished with that chamber of the heart.

For length measurement, the alignment and depth of the crystals are important. Most investigators use midwall or subendocardial shortening, as epicardial shortening is considerably less than either of the others. In addition, since the subendocardium is the portion of the myocardial wall most vulnerable to ischaemia, most investigators studying ischaemia use this location. It is important to verify the location of the crystals. Length crystals are aligned with the fibres of the heart to prevent twisting. In the mid-myocardium and subendocardium this means that they are placed parallel to the base of the heart.

The apical region of the heart shortens and thickens to a greater extent than the middle and basal portion, emphasizing the importance of obtaining control recordings and relating intervention measurements to them [11].

GLOBAL VENTRICULAR FUNCTION

An understanding of global ventricular function is required to understand regional ventricular func-

tion. Figure 1 presents pressure and volume characteristics of left ventricular contraction [15]. Ventricular emptying occurs only during the ejection phase of systole. Ventricular filling occurs during the filling phase of diastole. By definition, no change in volume occurs during isovolumic systole or diastole. The configuration of the volume curve is noteworthy. It resembles that generated by measures of regional function, with some important exceptions. During isovolumic systole, the left ventricle changes configuration; that is, it assumes a more spherical shape. This will result in shortening in some axes and simultaneous lengthening in others. Thus, the orientation of the measurement becomes crucial. Similarly, a change of shape in isovolumic relaxation could cause length changes in some axes of the heart. The former is far better defined than the latter.

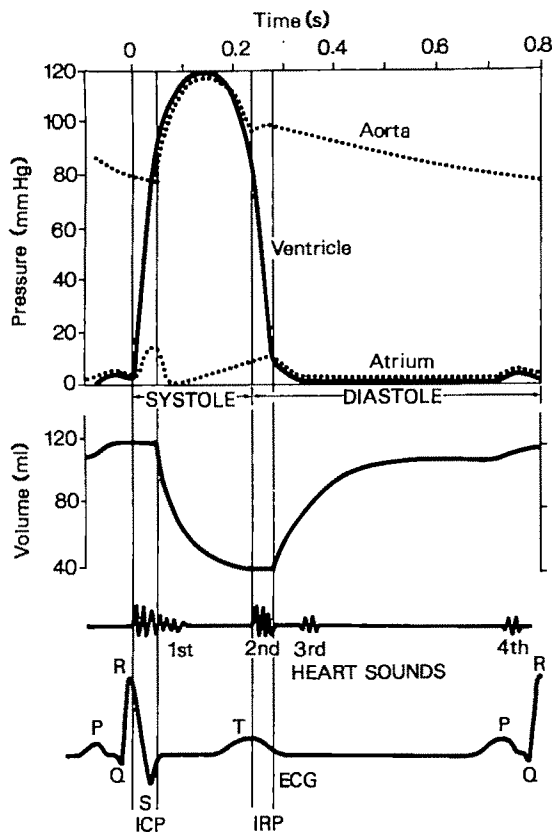


FIG. 1. Relationship of phases of heart contraction and relaxation to haemodynamics, ventricular volume, ECG and heart sounds. ICP = Isovolumic contraction period; IRP = isovolumic relaxation period. (From Smith and Kampine [15], with permission.)

REGIONAL VENTRICULAR FUNCTION

Normal

Figure 2 shows a schematic diagram of the heart during diastole and systole. We have arbitrarily outlined a section of the heart wall which represents the identical volume of myocardium. In our diagram, this is accomplished by keeping the area constant. In the bottom of the diagram, the length of the segment (L) is depicted in the left panel, and the thickness (T) in the right panel. As is obvious intuitively and from the diagram, the segment shortens and thickens during systole. It lengthens and thins during relaxation.

Ischaemic

Figure 3 depicts the same segment, now in a severely ischaemic state. For reference, the normal values are also presented. During diastole, the segment is longer and thinner than normal. When contraction occurs, this weakened or passive region is confronted with the pressure generated by the normal, non-ischaemic portion of the heart. Instead of shortening and thickening, it lengthens and thins further.

These diagrams explain why regional thickness and regional length measurements should be

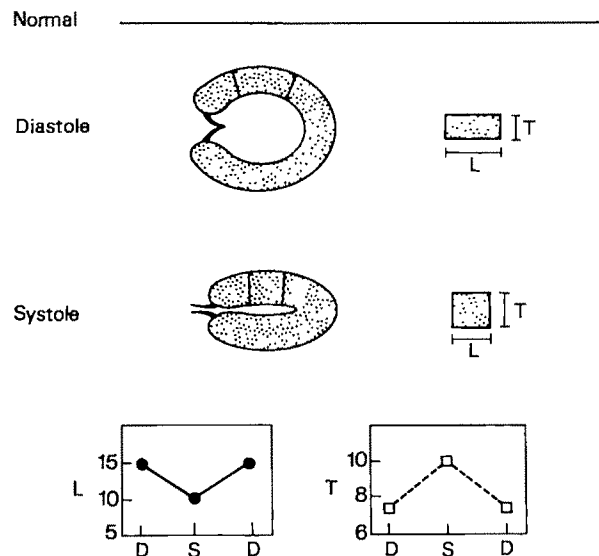


FIG. 2. Schematic diagram of normal regional ventricular wall motion. A segment will shorten and thicken during systole (S) and lengthen and thin during diastole (D). L = Length; T = thickness. The units are arbitrary, but are typical of length and thickness measurements in canine left ventricular muscle (in mm).

equally useful if performed equally well. They are measuring different dimensions of the same phenomenon of the same tissue.

Changes of function with progressive ischaemia are schematically depicted in figure 4 [12]. The

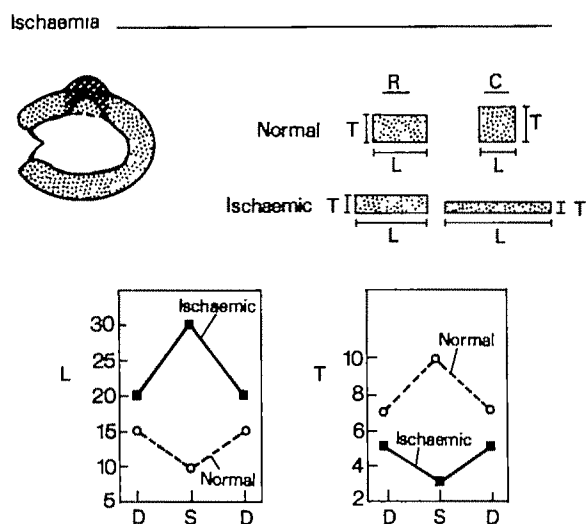


FIG. 3. Schematic diagram of ischaemic regional wall motion. Normal wall motion is displayed for reference. Motion of the ischaemic segment will be influenced by the interventricular pressures generated by that part of the heart contracting normally. Thus, it will bulge (lengthen and thin) during contraction (C), and shorten and thicken during relaxation (R). The striped area represents the ischaemic segment. T = Thickness; L = length; D = diastole; S = systole.

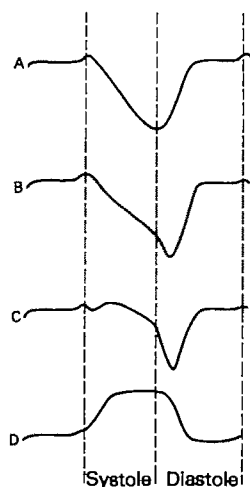


FIG. 4. Schematic diagram of regional length measurements during progressive myocardial ischaemia. Velocity of shortening decreases, post-systolic shortening occurs, and paradoxical lengthening occurs. (From Lowenstein and colleagues [12], with permission.)

initial changes consist of a decreased velocity of shortening with post-ejection, post-systolic, or early diastolic shortening. As ischaemia worsens, these two changes become greater, and systolic lengthening occurs.

Figure 5 shows actual recordings of the same series of events, but also clearly defines the isovolumic phases of systole [1]. It demonstrates that ischaemic systolic lengthening occurs only during isovolumic systole. It further demonstrates that a non-ischaemic region of the left ventricle (a "control segment") simultaneously has a longer end-diastolic length but a normal contraction pattern. Note also that the control segment does undergo dimension changes during isovolumic systole, as a result of the changes of global configuration mentioned above, but not during isovolumic diastole.

Using silastic-mercury length gauges, before development of sonomicrometry, it was thought that a 50% reduction of coronary blood flow was required to cause contraction abnormalities [18]. Vatner demonstrated that even a 10% reduction of coronary blood flow (CBF) was associated with a detectable decrease in function [17]. This is dramatic evidence of the exquisitely precise matching of CBF to myocardial metabolic need. It is therefore puzzling that many investigators use a 20–30% reduction in resting CBF as a control state in models of CAD utilizing a "critical stenosis," and yet report normal control regional function. Since a critical coronary stenosis is usually defined as one which limits or abolishes the hyperaemic response to transient coronary occlusion, and this is usually associated with a detectable decrease in control blood flow, it raises the possibility that regional ischaemia is present. This may explain some post-systolic shortening, which is often reported in the control state of the ischaemic segment.

Both length and thickness measured by sonomicrometry reflect the function of the location of the most ischaemic crystal. If the crystals are in a border zone or a zone with a transmural flow gradient, this may cause the area or degree of ischaemia to be overestimated [5].

The effect of loading conditions upon ischaemic and non-ischaemic segments has not been completely studied. Two groups have recently studied the effect of preload. In normal myocardium, end-diastolic length changes with preload, but percent systolic shortening remains constant. In ischaemic segments, end-diastolic length increases, systolic

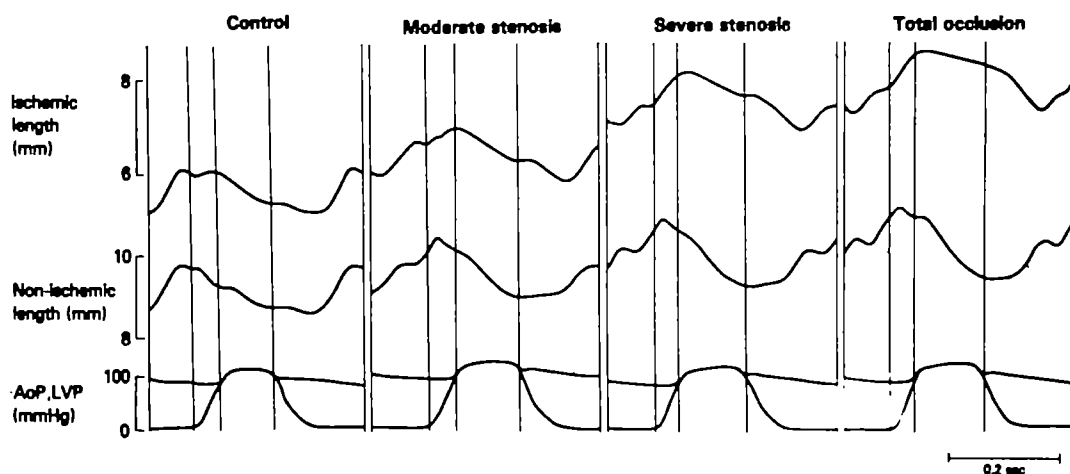


FIG. 5. Analogue recordings of regional length measurements during progressive myocardial ischaemia. Note that paradoxical lengthening occurs only during the isovolumic phase of systole, and only in the ischaemic segment. (Reproduced from Akaishi, Schneider and Mercier [1], with permission.)

shortening and post-systolic shortening decrease, and the magnitude of the paradoxical lengthening decreases [7]. Paradoxical lengthening is passive, and post-systolic shortening in severely ischaemic myocardium appears to occur primarily or exclusively by elastic recoil. The magnitude of bulging and post-systolic shortening are therefore dependent upon loading conditions [2].

Aortic constriction was shown to be associated with unchanged systolic shortening in the apical and mid-ventricular region, but decreased shortening at the base. The end-diastolic length was increased in the former regions, but unchanged at the base [11]. The effect of afterload upon regional function of ischaemic areas has not been completely clarified.

DIFFERENTIAL REGIONAL RESPONSES TO AN INTERVENTION

In order to compare responses of an intervention (such as administration of an anaesthetic) upon heart regions which are supplied by a normal coronary artery with one supplied by a narrowed artery, it must first be established that all regions will respond in similar ways in the absence of narrowing. That this is true is shown by our initial

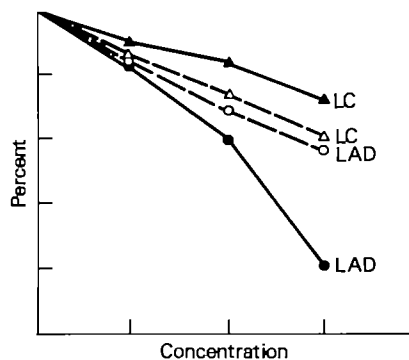


FIG. 6. Systolic shortening in the left anterior descending (LAD) and circumflex coronary artery territories were similarly effected by increasing concentrations of halothane before constriction of a canine coronary artery. After the left anterior descending coronary artery was critically constricted, the identical concentrations of halothane caused a further decrease of systolic shortening in the LAD territory, whereas shortening was preserved (and tended to be enhanced) in the circumflex territory supplied by a normal coronary artery. (From Lowenstein and colleagues [12], with permission.)

studies of the effect of halothane in the dog [12] (fig. 6). The decrement of systolic shortening with increasing halothane concentration was similar in the regions supplied by the left anterior descending and circumflex coronary arteries. After

narrowing of the LAD coronary artery, no changes in contraction were observed in either segment under control conditions (0.5% halothane). However, we observed contraction patterns characteristic of ischaemia when halothane concentration was increased and aortic pressure decreased [12]. In a subsequent study, we demon-

strated the invariable association of disproportionate reduction of regional coronary blood flow whenever these abnormal wall motions were observed, establishing a cause and effect relationship which has been confirmed a number of times [6].

These abnormalities (inhomogeneities) occur

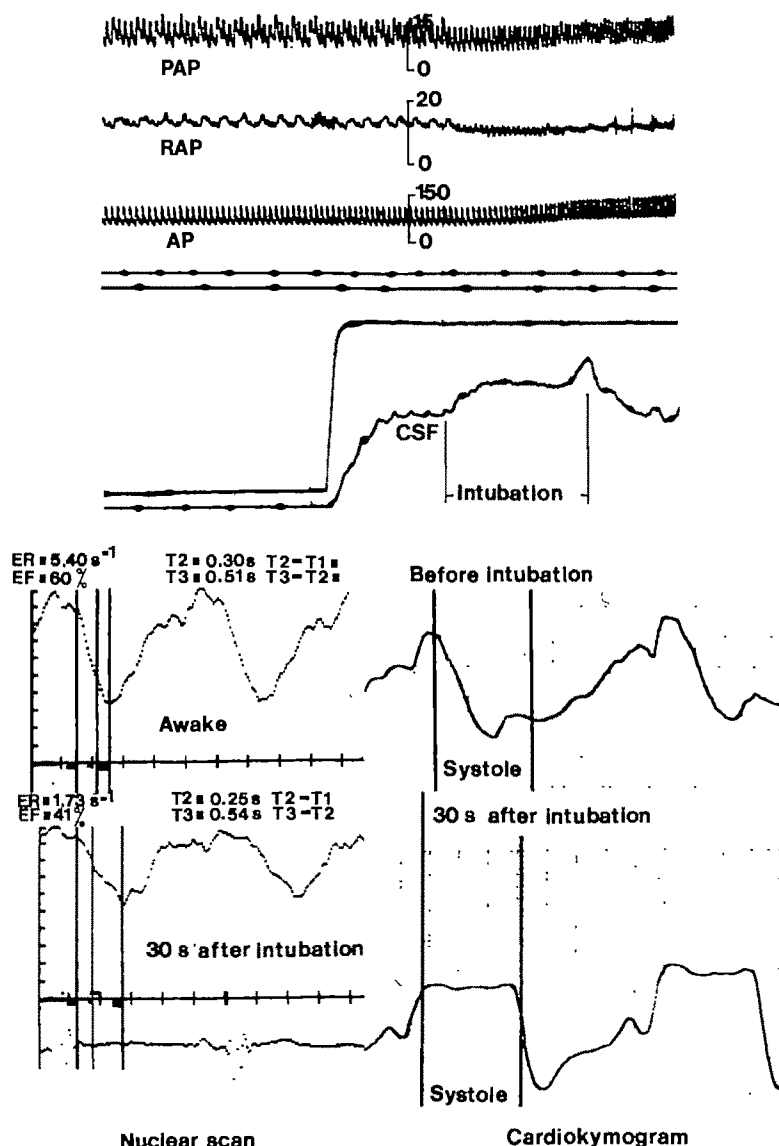


FIG. 7. ECG, coronary sinus blood flow (CSF), cardiokymogram, haemodynamics and blood pool scintigram from a patient with severe CAD undergoing endotracheal intubation. Note abnormal ventricular wall motion indicated by the cardiokymogram, decreased left ventricular ejection fraction indicated by scintigram, and decreased coronary sinus blood flow precipitated by tracheal intubation without haemodynamic change. These data suggest myocardial ischaemia on the basis of coronary artery vasomotion. They support the hypothesis that ventricular wall motion abnormalities in man are caused by myocardial ischaemia. (From Lowenstein and Reiz [13], with permission.)

because of differential strength of contractile potential. In unpublished studies, Dr Gillian Geffin perfused a coronary artery with citrated but oxygenated blood. She noted identical changes in regional function as with ischaemia, as a result of calcium ion binding rather than reduced flow of oxygenated blood. This indicates the changes are not entirely specific. However, when an intervention is administered systemically or globally (drug, haemodynamic changes, etc.), one area of the heart demonstrates characteristic changes and reversal occurs with cessation of the intervention or treatment, the changes are highly suggestive of regional myocardial imbalance.

REGIONAL FUNCTION MEASUREMENT IN MAN

Ultrasonic crystals have been used in man by several groups of investigators, including the groups led by Hagl and Heimisch at the Deutsches Herzzentrum, Munich [8], Wechsler at Duke University [9] and Moores at University of California, San Diego [14].

Hagl and associates [8] noted improvement of contraction after myocardial revascularization in nine of 11 patients with unstable angina pectoris. Temporary occlusion of the graft was associated with decreased regional function, including paradoxical contraction during graft occlusion in one patient [8]. These studies suggested that changes of ischaemia were similar to those observed in experimental animals.

Wohlgelehrter and associates recently studied the effect of the occlusion of a coronary artery during percutaneous angioplasty in man using two-dimensional echocardiography [19]. They divided the apical-long axis view of the heart wall into 100 equidistant cords, and analysed thickness at the largest and smallest volume using a centre-line method. They also demonstrated that the changes in regional function when a coronary artery was occluded by inflating the balloon were of a similar character and sequence as in experimental animals.

During anaesthesia and during and after cardiac and vascular surgery, scintigraphy, echocardiography and cardiokymography (CKG) have been used to document regional wall motion abnormalities. Thallium scintigraphy has been used to demonstrate regional blood flow heterogeneity.

The striking part of these studies is that wall motion abnormalities are far more common than

ECG changes [3, 10, 15]. Some interpret this to mean that ischaemia is more frequent than is recognized by other methods, others that wall motion abnormalities are not specific and often do not indicate ischaemia. Figure 7 shows data from a patient with CAD in whom coronary sinus blood flow, the CKG, ECG, and blood pool scintigraphy were studied during tracheal intubation [13]. Note that the decrease in CBF was congruent with the abnormal wall motion and lower ejection fraction, strongly suggesting an ischaemic aetiology, and lending added credence to those who use wall motion abnormalities as a highly specific marker of ischaemia.

CONCLUSION

Regional wall motion abnormalities are sensitive and highly, but not entirely, specific indicators of myocardial oxygen imbalance. Their measurement provides a powerful tool for animal experimentation and clinical detection of myocardial ischaemia. Further research is required to define those situations in which regional contraction abnormalities occur despite normal tissue oxygenation, and their mechanism.

ACKNOWLEDGEMENT

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THE PRESSURE-LENGTH LOOP

P. FOËX, C. M. FRANCIS, G. R. CUTFIELD AND B. LEONE

Regional left ventricular wall motion is easily measured by sonomicrometry. Dimension transducers can be placed in the epicardial, middle or endocardial portion of the ventricle to measure segment length, on opposite walls to measure diameter, or on the epicardium and the endocardium to measure wall thickness [3, 11, 23, 29]. Analysis and interpretation of dimension signals may be difficult because of the need to determine the exact timing of end-diastole, onset of ejection, and end of ejection. This is only possible when aortic blood flow and aortic pressure are measured at the same time in the immediate vicinity of the aortic valve. Otherwise transmission delays occur and the timing of these events becomes inaccurate.

Examination of the instantaneous relationship between pressure and dimensions, the pressure-dimension loop, partly overcomes the need to use signals other than pressure and dimensions to determine the timing of end-diastole, onset and end of ejection because they correspond to obvious features of the loop (fig. 1). Moreover, pressure-dimension loops provide additional information regarding synchrony or asynchrony of contraction, segmental work and regional contractility. This brief review will consider only the pressure-length loop.

SHAPE OF PRESSURE-LENGTH LOOPS

Pressure-length loops consist of four segments corresponding to isovolumic contraction, ejection, isovolumic relaxation and ventricular filling (fig. 1). In the normal heart, most pressure-length loops are approximately rectangular (fig. 2A). However, because of the complexity of the geometry of the left ventricle, some regions may exhibit early shortening (fig. 2B), or early short-

ening followed by early lengthening (fig. 2C) so that the isovolumic phases of the cardiac cycle may not be isometric. These features are explained by a reduction or an increase in area of the inner surface of the left ventricular cavity. During isovolumic contraction the ventricle becomes more spherical and the area tends to decrease, while during isovolumic relaxation the ventricle becomes more ellipsoidal and the area tends to increase [13]. Furthermore, differences in regional contraction patterns have been observed depending upon the location of the length transducers. Extent of shortening and patterns of wall motion differ between the long and short axis, and also between apical and basal regions [12]. Thus pressure-length loops may manifest different characteristics depending upon which region of the ventricle is examined.

Pressure-length loops may appear to lean to the right (fig. 2D). This is usually caused by ischaemia [5, 29], and results from lengthening during isovolumic contraction and shortening during isovolumic relaxation (post-systolic shortening). Systolic lengthening represents displacement

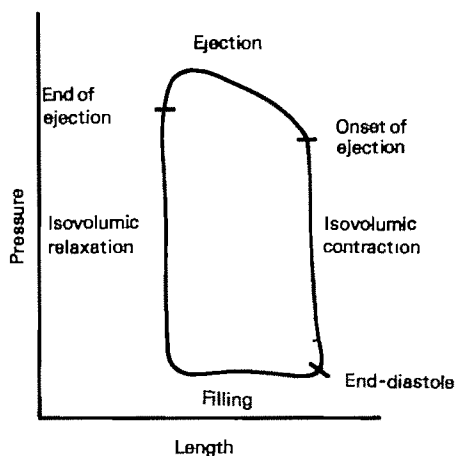


FIG. 1. Pressure-length loop obtained in the left ventricle showing its relation with the phases of the cardiac cycle.

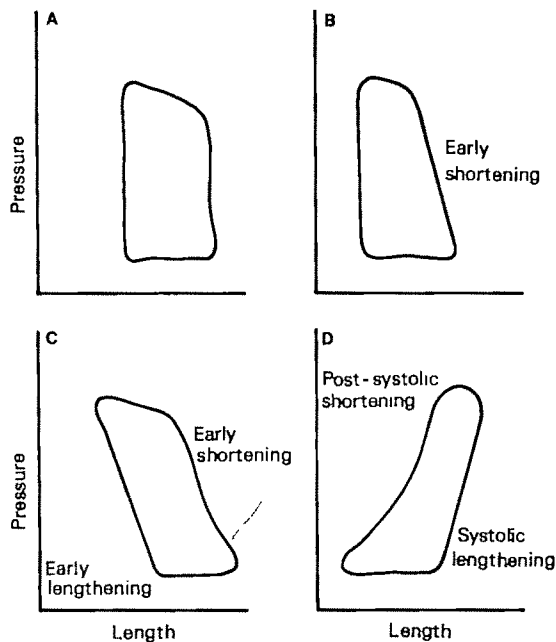


FIG. 2. Three pressure-length loops (A, B, C) are representative of normal regional contraction in the left ventricle. Panel D is representative of left ventricular asynchrony. Asynchrony is usually, but not exclusively, caused by myocardial ischaemia (see text for details).

forced upon the abnormal segment by normal neighbouring segments. This may be caused by a delay in electrical activation [14], or a change in preload tension in the ischaemic region [1]. Post-systolic shortening may represent active shortening that is not contributing to pump function because it occurs after the end of ejection, or pure elastic recoil. With extreme ischaemia the pressure-length loop is even more distorted (fig. 3). Examination of the pressure-length loops make it obvious that the total length change may be partly or fully a result of paradoxical wall motion.

The controversy surrounding the possibility of enhanced function of the normal myocardium when a limited area becomes ischaemic, may be partly resolved by examination of pressure-length loops [15]. As the ischaemic area lengthens during isovolumic contraction, some of the normal myocardium must shorten. While total shortening may increase, ejection shortening may remain unchanged (fig. 3). The early shortening merely causes the transfer of blood within the left ventricle away from the normal area into the ischaemic area. It does not necessarily reflect enhanced function.

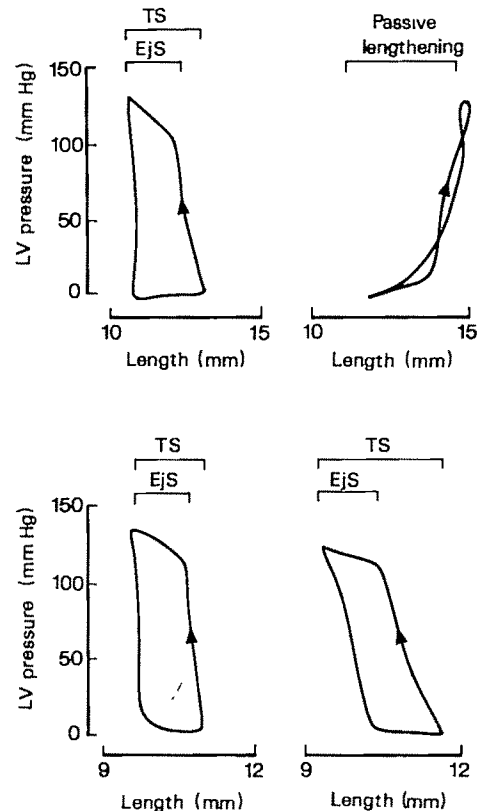


FIG. 3. When a coronary artery is abruptly occluded, the normal pressure-length loop of the dependent segment (top left) becomes distorted (top right) and most of the dimensional length change represents passive lengthening followed by elastic recoil. In neighbouring normal segments, the pressure-length loop, previously rectangular (bottom left), is also modified and leans to the left (bottom right). Its total shortening (TS) increases but ejection shortening (EJS) does not.

Abnormal pressure-length loops have been observed in the absence of ischaemia during studies of the interactions between the calcium channel blocker verapamil and the inhalation anaesthetics halothane and isoflurane. In the absence of reduction of coronary flow, these observations suggest that pressure-length loops may lean to the right because of asynchrony of ventricular contraction as a result of altered excitation-contraction coupling, rather than ischaemia [19, 31].

AREA OF THE PRESSURE-LENGTH LOOP: AN INDEX OF SEGMENTAL WORK

The area of the pressure-volume loop represents ventricular stroke work. By analogy, the area of

the pressure-length loop may be regarded as an index of regional work. However, because it has units of pressure and length and not pressure and volume, it is only an index of segmental work [6, 18, 24, 30]. Increases in preload increase the loop area and make it possible to obtain regional ventricular function curves (fig. 4). Positive inotropic interventions shift the regional function curve upwards and to the left [8].

Interpretation of the area of the pressure-length loop may be difficult when contraction is abnormal (fig. 5). When the loop leans to the right, its area encompasses three regions:

- (1) The region corresponding to systolic lengthening. This obviously represents work done *on* the segment, as opposed to work done *by* the segment.
- (2) The region delineated by post-systolic shortening. This represents either active work or work caused by elastic recoil. However, it is ineffective in terms of ventricular pump function as it does not contribute to ejection.
- (3) The middle region of the loop, the only region which represents work contributing to pump function. The ratio of this area to the whole area gives an approximation of the effective contribution of the segment to ejection. In severe ischaemia the area may become negative when the loop is described in an anticlockwise fashion (fig. 3).

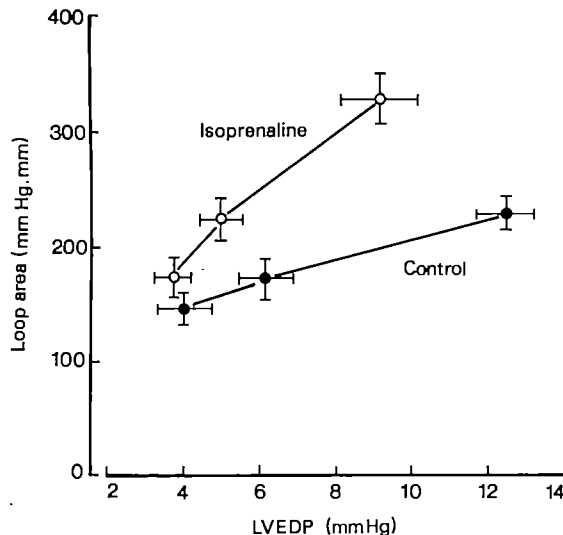


Fig. 4. Regional left ventricular function curves may be constructed by plotting the loop area against left ventricular end-diastolic pressure. Positive inotropic interventions (isoprenaline) shift the curve upwards and to the left [8].

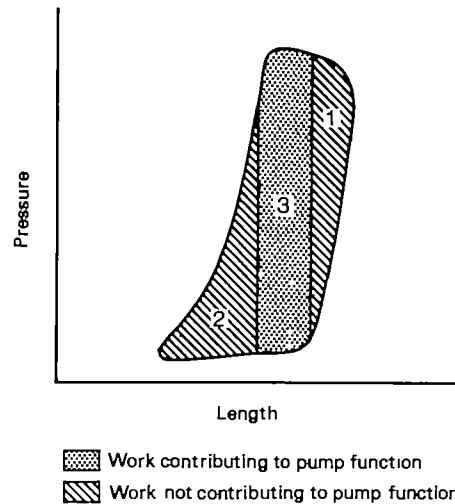


Fig. 5. When segmental asynchrony is present only a fraction (3) of the total loop area (1+2+3) represents the work the segment contributes to left ventricular pump function (see text for details).

END-SYSTOLIC PRESSURE-LENGTH RELATIONSHIPS: AN INDEX OF REGIONAL CONTRACTILITY

In 1895, Otto Frank used the pressure-volume relationships in the frog's heart in his detailed analysis of cardiac contraction [10]. More recently, the pressure-volume relationships at the end of systole have been extensively studied in perfused isolated left ventricle preparation and in the intact heart [20, 25, 26]. At the end of systole there is a linear relationship between pressure and volume that is very sensitive to inotropic interventions (fig. 6).

Suga and his colleagues [27] developed the concept of time-varying elastance: wall stiffness increases during systole and decreases during diastole. This concept has been extensively studied, and the end-systolic pressure-volume relationship is considered to be insensitive to changes in preload and afterload. Thus, the pressure-volume line at end-systole has been regarded as an index of contractility independent of preload and afterload [21]. This concept has been challenged and recent evidence suggests that altered resistance [17], and changes in preload [8] may influence the slope of the end-systolic pressure-volume relation. Changes in inotropy may cause not only a change in slope but also a shift of the end-systolic pressure-volume line [9, 22].

By extending the concept of time-varying

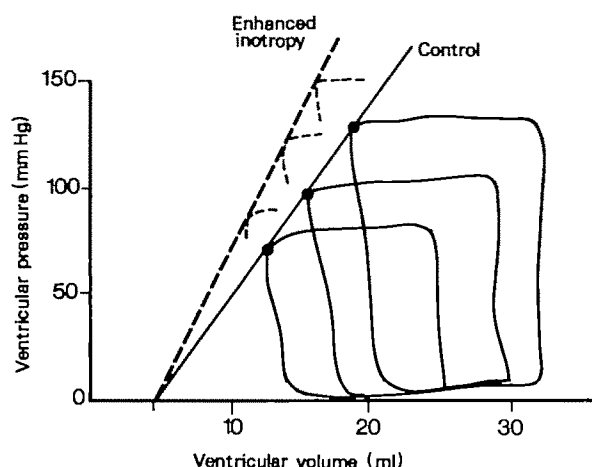


FIG. 6. Analysis of pressure-volume loops has shown that at end-systole, pressure-volume points (O) obtained by changing outflow pressure, fall on a straight line, the end-systolic pressure-volume line. Enhanced inotropy increases the slope of this line. Early work suggested a unique volume at zero pressure [27].

elastance to pressure-length relationships, it can be shown that a linear relationship exists between pressure and diameter [4, 16], and pressure and length at the end of systole ($P-L_{es}$) (fig. 7) and that increases in inotropy increase its slope (fig. 8) [7, 8]. However, myocardial depression may cause a shift of the line towards larger dimensions, but without change in slope (fig. 9) [8, 9]. It must be noted that end-systolic pressure-length relationships can be obtained either by increasing afterload or by increasing preload. Although both

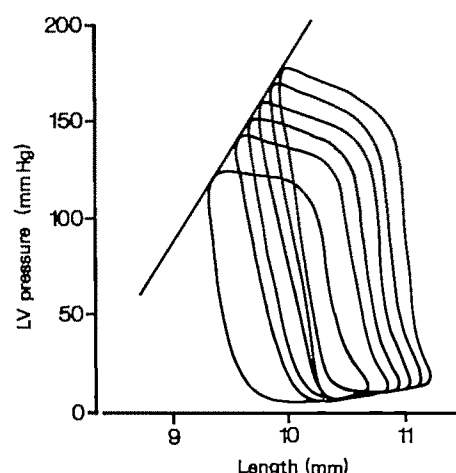


FIG. 7. When arterial pressure is increased by an infusion of phenylephrine, the end-systolic pressure-length co-ordinates of each cardiac contraction fall on a straight line, the end-systolic pressure-length line.

interventions increase end-systolic pressure and length, the slope of the $P-L_{es}$ is always flatter when preload, as opposed to afterload, challenges are applied in order to generate the end-systolic pressure-length points. Thus for the intact heart, the way in which changes in pressure and length are obtained influences the slope of the $P-L_{es}$ [2, 8]. Interpretation of the data must take into account the way in which pressure was altered.

An early tenet of the analysis of end-systolic pressure-dimension relationships was that a constant volume or dimension intercept exists at zero pressure (figs 6, 8) [27]. This has been subse-

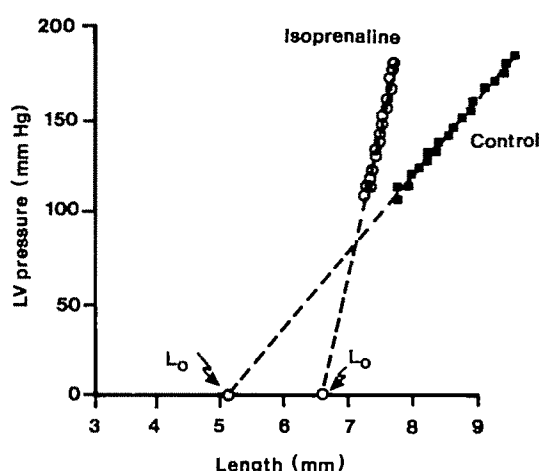
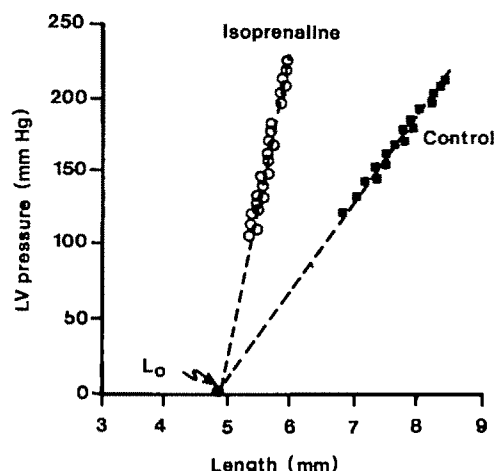


FIG. 8. Positive inotropic interventions increase the slope of the end-systolic pressure-length line. The length intercept may (left panel) or may not (right panel) be unique [7].

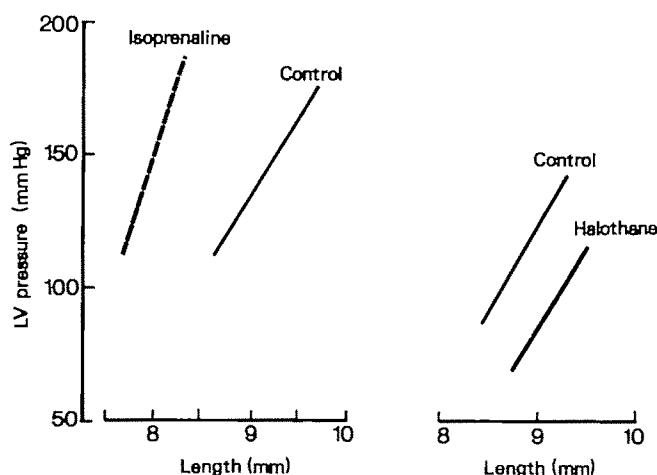


FIG. 9. While positive inotropic interventions increase the slope of the end-systolic pressure-length relationship (left hand panel), negative inotropic interventions (such as the addition of halothane to pentobarbitone) may cause a shift to the right without change in slope (right hand panel) [9].

quently disproved [4] and, at regional level, the intercept of the $P-L_{es}$ line with the length axis is not constant [8].

Another tenet is that increases and reductions in loading have the same effect. This is not confirmed in the intact heart where, after a rapid reduction in afterload, the end-systolic pressure-length co-ordinates do not immediately fall on the $P-L_{es}$ line: the length remains longer for several beats (fig. 10). This indicates that the viscoelastic properties of the myocardial segment influence the end-systolic pressure-length relationship. The passive stretch of the segment, demonstrated by the rightward displacement of the loop, results in hysteresis. However, when the preload is high,

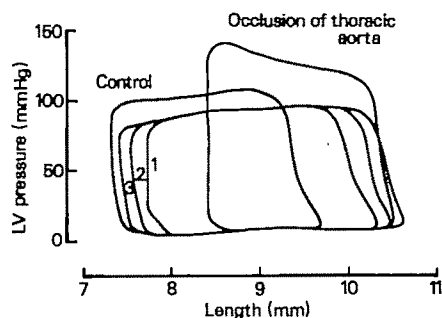


FIG. 10. Series of pressure-length loops generated by partial aortic occlusion. The first loop (1) after releasing the occlusion is to the right of the control loop. This demonstrates that a decrease in pressure does not have the same effect on the pressure-dimension relationships as does an increase in pressure [32].

the initial fibre length utilizes all potential passive stretch and hysteresis does not occur [32].

Severe regional myocardial ischaemia limited to a small area of the left ventricle renders the analysis of the end-systolic pressure-length relationships almost meaningless [28]. In these circumstances pressure reflects the global ability of the ventricle to develop tension, while changes in regional dimensions are determined by the viscoelastic properties rather than the performance of

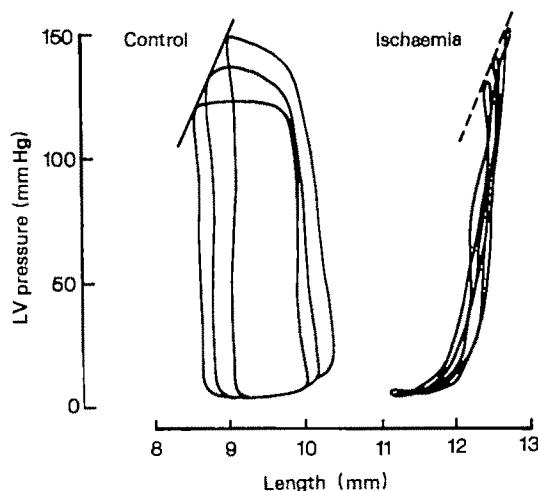


FIG. 11. When a segment is rendered ischaemic, the loop is deformed and the end-diastolic length may be greatly increased. Provided the ischaemic area is small, the remainder of the left ventricle is able to develop pressure and the slope of the end-systolic pressure-length line may remain essentially unchanged.

the ischaemic segment. The end-systolic pressure-length co-ordinates may continue to fall on a straight line, and the slope may remain almost unchanged even though active contraction has ceased (fig. 11).

Examination of the pressure-length loop greatly facilitates detection of segmental asynchrony. The contribution of the segment to pump function can be appreciated by assessment of the *effective* loop area. Assessment of regional contractility based on the end-systolic pressure-length relationship is also possible. However, depending upon the level of contractility, changes in slope or shifts of the end-systolic pressure-length line may occur. Moreover, analysis of the end-systolic pressure-length relationship must take into account the way in which pressure has been altered.

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LOCAL FORCES IN THE MYOCARDIUM

J. L. THEISSEN, P. P. LUNKENHEIMER, K. REDMANN, G. FRIELING, N. STROH AND A. LUNKENHEIMER

With the clinical methods available for determining myocardial performance it is not possible to distinguish between global ventricular heart failure and an imbalance in segmental myocardial function, such as occurs in ischaemic heart disease. In today's climate of non-invasive diagnostic methods, even during open heart surgery it is not acceptable to obtain any kind of comparison between local myocardial forces and segmental length changes by means of intramyocardial monitoring. Nevertheless, our method of measuring local forces in the myocardium has been developed so that measurements can be made routinely during heart surgery and after operation.

THE PROBE

Figures 1 and 2 show a local force probe, 1.2 mm in diameter and 9 mm long, as described by Lunkenheimer and his colleagues [5]. Near its tip there is a window which exposes a flexible bar, the deviation of which is sensed by a strain gauge. When the needle is inserted to the myocardium, myocardial fibres slip on to the flexible bar and evoke an electrical signal which is proportional to the tension in the myocardial fibres spread by the probe. The tension measured is not, however, the longitudinal strain, but the perpendicular force produced by displacing fibres from their original stretched position.

Technically, the method is a quasi-isometric measurement [3]. The bar deviation is 10 μ m at a maximal signal of 150 mN, which is greater than any we have recorded. Unlike other probes, such

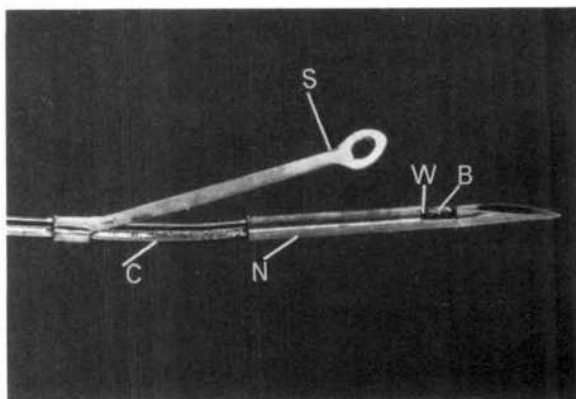


FIG. 1. The local force probe. It is a 1.2-mm thick, 9-mm long needle with a window near the tip of the probe. An inner flexible bar is exposed by the window. Its deviation into the centre of the needle is sensed by a strain gauge. N = Hypodermic needle (outer tube); W = lateral window; B = flexible bar; C = PE-catheter; S = butt strap to fix the probe.

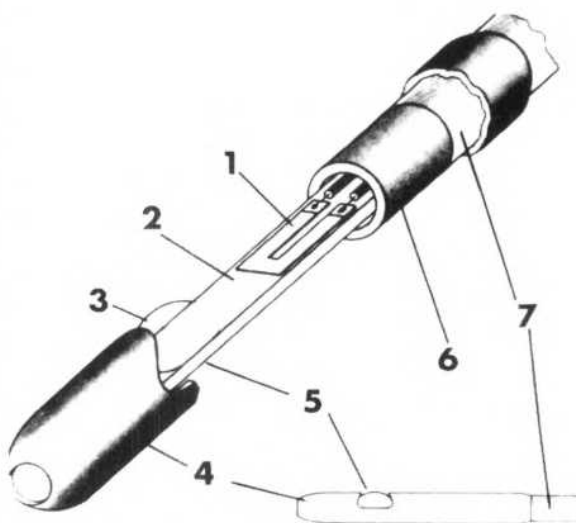


FIG. 2. Exploded view of the force probe. 1 = Strain gauge; 2 = flexible bar; 3 = promontorium = in the window exposed part of the flexible bar; 4 = outer tube; 5 = lateral window; 6 = bar support; 7 = PE-catheter.

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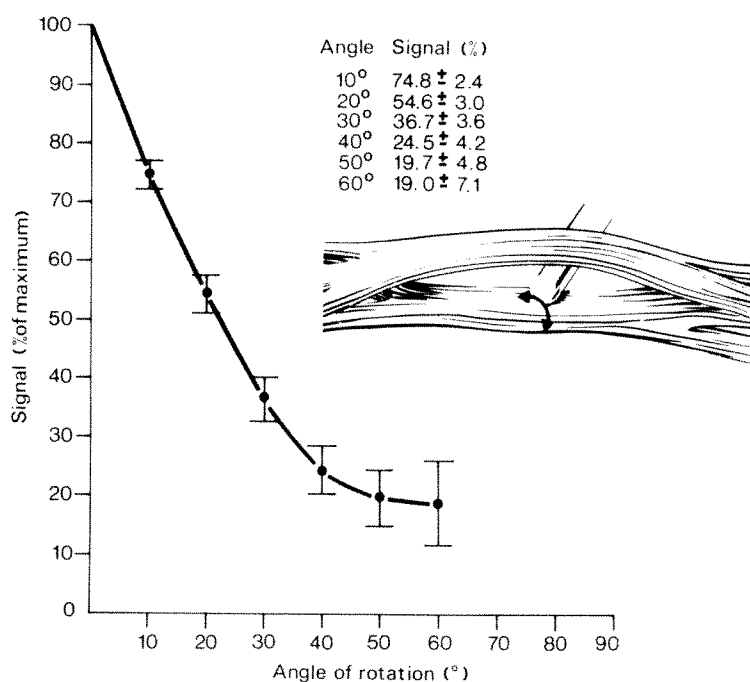


FIG. 3. Rotational sensitivity of the force probe. Loss in signal amplitude (% control) with angular deviation from optimal orientation.

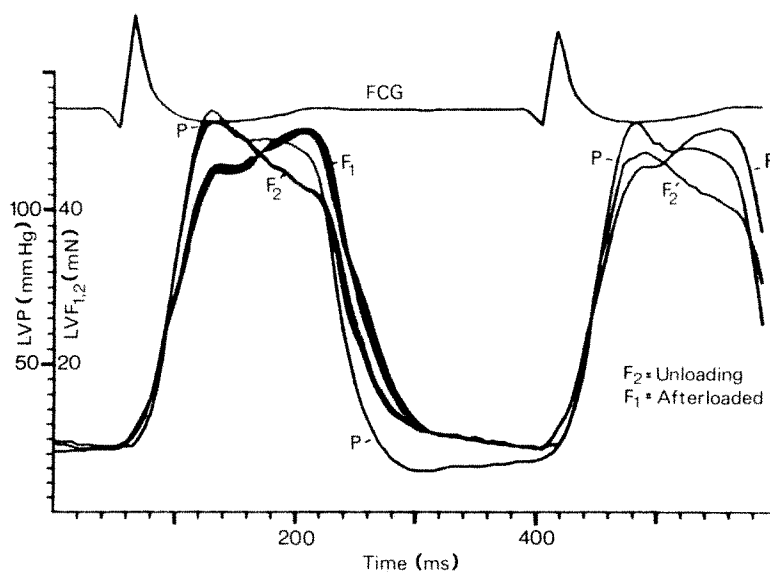


FIG. 4. ECG, Left ventricular pressure (LVP, P) and the two different types (F_1 , F_2) of left ventricular force (LVF) signals generated within the ventricular myocardium. F_1 follows the typical "afterloaded" force type, ascending during the ejection period. F_2 is an "unloading" curve which descends during ventricular ejection.

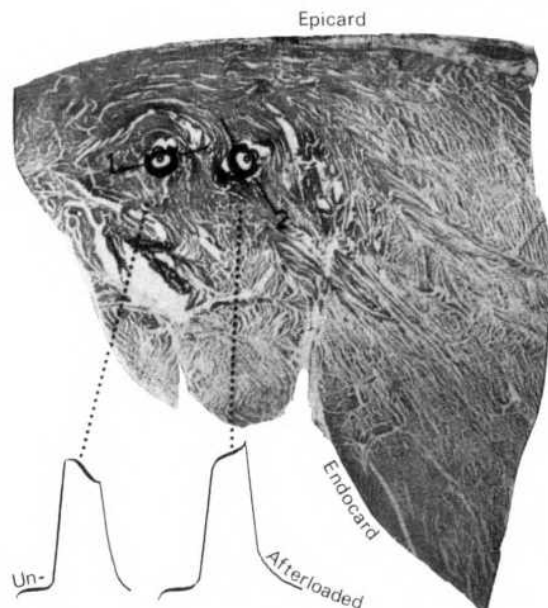


FIG. 5. Implantation sites of the probe: afterloaded signal is measured when the probe is coupled to oblique transversally oriented fibres whereas the unloading (Un-) signal emerges from areas where the fibre orientation is parallel to the ventricular surface.

as those described by Walton's team [9], our needle probe does not have to be fixed by suture because it is adequately held by the fibre meshwork. Little trauma is caused and less than 100 mg of muscle is damaged, provided the coronary arteries are avoided. Figure 3 shows that the signal is maximal when the window is parallel to the mean force trajectory. The orientation of this force vector is determined by rotation of the probe around its long axis. This rotational sensitivity allows a precise assessment of local force trajectories, as previously reported [7], albeit without histological confirmation.

The geometry of implantation varies greatly from place to place in the myocardium, producing a variable preloading of the fibres. This preload, caused by spreading the local myocardial network, depends on the local branching density in relation to the probe's geometry, and makes it necessary for the force trajectory to be expressed as a percentage of a control value which is determined before each event rather than in absolute units.

CARDIODYNAMIC RESPONSES

Lunkenheimer and his colleagues [5, 7, 8] first used this method to investigate cardiodynamic

responses. This revealed that two different types of force signal were generated within the intact ventricular myocardium: an unloaded type which decreases in force during the ventricular ejection period, and an afterloaded type which increases during the ventricular ejection period (fig. 4). The respective incidence of the two types in all implantations is 9:1. Using histology, we found that the afterloaded signals were associated with oblique transversally orientated fibre bundles (fig. 5). The unloaded signals emerged from areas where the fibre orientation was parallel to the ventricular surface.

In accordance with Laplace's law, the tension in surface parallel fibres, that is the unloading type of signals, decreases during ventricular contraction. Shortening of transmural fibres tends, however, to be inhibited during systolic wall thickening, so that there is an increase in tension throughout the whole period of contraction, which produces the afterloaded type of signal.

If the ventricular diameter increases, its wall naturally becomes thinner and the transmural fibre components become rearranged in a more tangential direction, reducing their transmural force component. As a result, during an acute

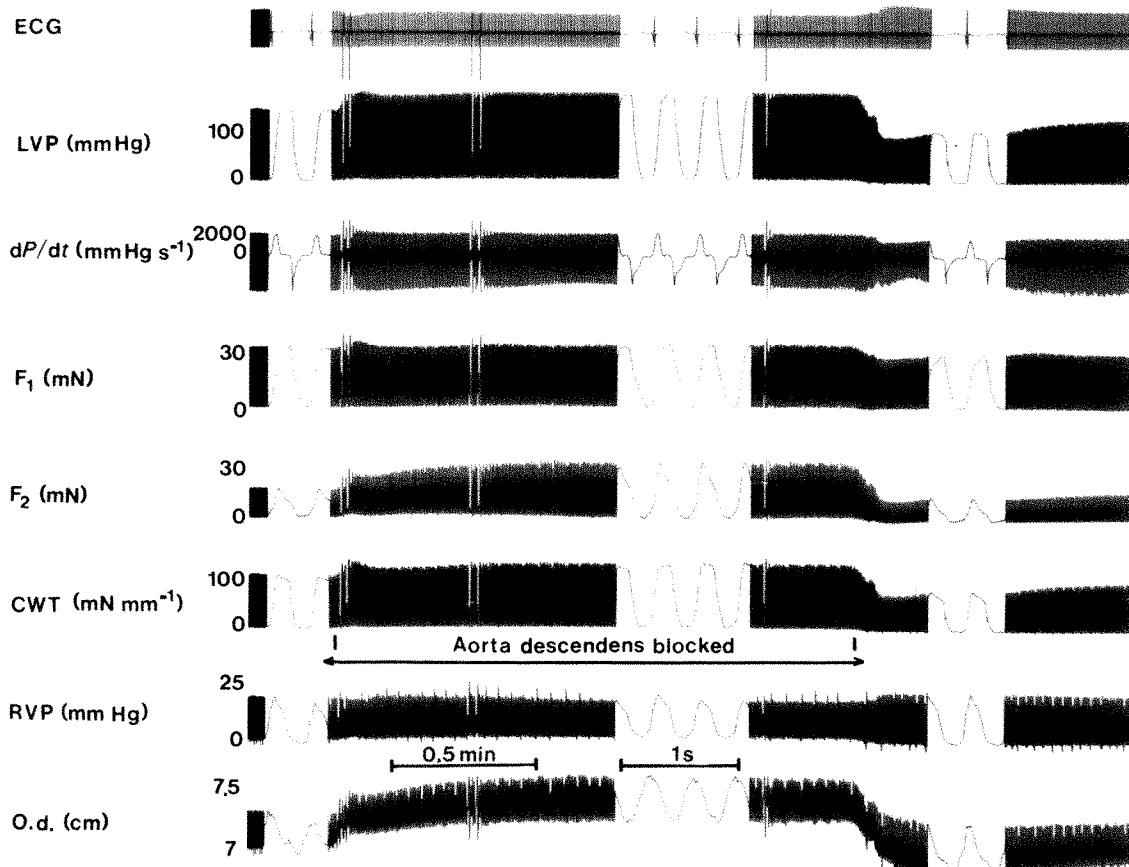


FIG. 6. Local force changes following inflation of a balloon in the ascending aorta. ECG = Electrocardiogram; LVP = left ventricular pressure; F_1 , F_2 = local forces; CWT = calculated wall tension; RVP = right ventricular pressure; o.d. = outside diameter.

increase in left ventricular afterload, which may occur during hypertensive crises, or, as in figure 6, during the experimental inflation of a balloon catheter in the ascending aorta, the wall tension is increased. However, our results show a substantial increase in the unloading type of local force, but not in the afterloaded type. Thus what has really happened is that the ventricular diameter has increased and the wall thickness has decreased. The oblique transmural fibres have been given a more surface-parallel orientation. The internal load [6] originating from their transmural force vector is likely to be reduced. So the general increase in ventricular wall tension is probably partly counteracted by a release from internal load in this fibre population. As a result of these two opposing effects, we record a restricted response in this muscle compartment.

PHARMACOLOGICAL STUDIES

Our aim was to develop a method of measuring the inotropic effects of drugs separately from variations in pre- and afterload. The coupling conditions of our needle probe make our method dependent on the loading conditions of the whole myocardium, that is, on its size. Under experimental conditions, however, the global ventricular load can be kept constant, by inflating a balloon in the ascending aorta, for example. This is suitable for examining drugs which also produce a decrease in peripheral resistance. A more sophisticated approach is to inject the drug to a coronary artery, provided the dose is small enough to avoid a global effect on the heart and peripheral vascular system. By having probes both in the irrigated zone and in a control area, comparisons can be ensured.

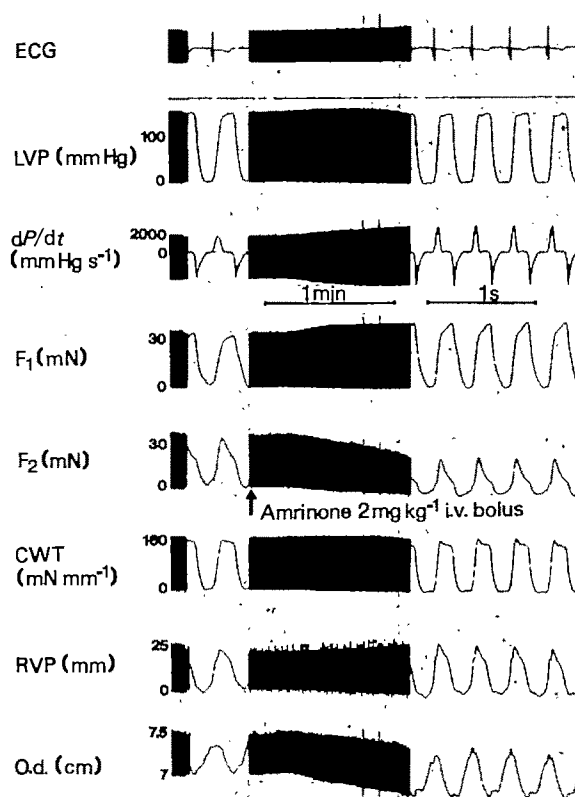


FIG. 7. Haemo- and cardiodynamic changes after an injection of amrinone 2 mg kg^{-1} i.v. (Abbreviations as figure 6.)

Amrinone may be cited as an example of a drug producing the complex cardiodynamic response including simultaneous changes in inotropy, pre- and afterload [1, 2, 4]. One would expect an increase in wall tension from the administration of this positive inotropic drug, but figure 7 shows a decrease in the unloaded force and a small increase in the afterloaded force. This can be explained on the grounds that amrinone reduces the peripheral vascular resistance and increases the venous capacitance, so that the pre- and afterload decrease, the left ventricular diameter decreases and wall thickness increases. According to Laplace's law, the tension in the surface-parallel fibres decreases, despite the positive inotropic stimulation. The afterloaded force signal increases more or less in parallel with the increase in wall thickness.

Perhaps this kind of indirect proof of the inotropic effect of amrinone is not convincing, but figure 8 shows what happens when amrinone is injected to the distal circumflex artery. The local forces at positions F_3 and F_4 , downstream of the

circumflex artery, increase, whereas at control positions F_1 and F_2 no changes are seen. The shortening distance of the perfused segment increases, but the diastolic geometry of the segment does not change, which means that the preload of this segment remains constant. Thus even substantial changes in segmental inotropy such as an increase of up to 30% in local forces, are not transmitted to the global ventricular function if the area involved is smaller than the territory perfused by the whole circumflex artery.

CONCLUSION

Thus the tension in the myocardial wall does not exist merely as described by Laplace's law. There are also inhomogeneities in ventricular wall tension which result from the interplay of two force components. As the two components are sensitive to changes in ventricular geometry, the only way to use the method as a pharmacological tool is to make segmental measurements after intracoronary drug administration and compare them with

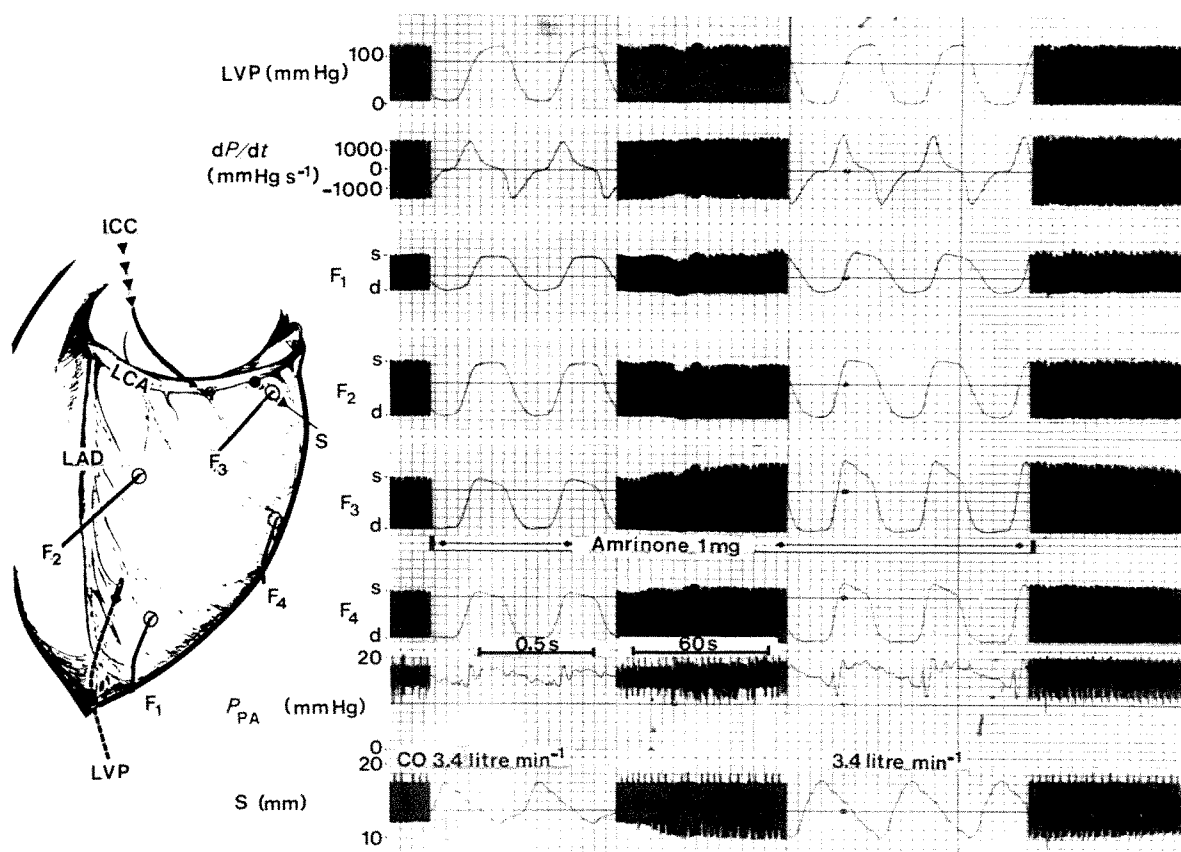


FIG. 8. Cardiodynamic changes after an injection of amrinone 1 mg to the distal circumflex artery. CO = Cardiac output; F_1 – F_4 = positions of local forces; ICC = intracoronary catheter; LCA = left coronary artery; LAD = left anterior descending artery; LVP = left ventricular pressure; P_{PA} = pulmonary artery pressure; S = segmental shortening.

measurements from a control segment. The experimental situation is then comparable to that of an “*in situ* isolated” preparation of a myocardial segment.

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USE OF THE WALTON-BRODIE STRAIN GAUGE ARCH TO MEASURE CONTRACTILE FORCE DURING ANAESTHESIA

J. G. REVES AND J. K. PRUETT

The measurement of myocardial contractility has been and remains elusive. A method of directly measuring contractile force by means of a strain gauge sutured to the myocardium was pioneered by R. P. Walton and O. J. Brodie [28]. It is particularly noteworthy that Walton was a physician and pharmacologist whose primary interest was cardiovascular pharmacology, and he and his associates working at the Medical University of South Carolina have had a long, productive interest in the effects of anaesthetic drugs on the myocardial contractile force. The purpose of this paper is to describe the method of measurement of contractile force and review the use of the strain gauge arch in extending our knowledge concerning the effects of anaesthetic drugs on myocardial contractility. There has been one previous review of the strain gauge arch (SGA) and its use in anaesthesia research [7].

METHODS

The Walton-Brodie strain gauge arch used to record the force of myocardial contraction (CF) consists of a strain element bonded to an arch with feet that can be sutured to the myocardium. Electronically, the strain gauge element acts as one leg of a Wheatstone bridge and when the wire within the element is stretched by the muscle contraction the resulting change in resistance produces an imbalance in the bridge current which is sensed by an amplifier and recorded. The construction and sensitivity of the SGA is such that actual displacement of the feet of the arch by the contracting muscle is almost imperceptible, thereby providing the basis for recording iso-

metric contractions. The most commonly used arch has the strain gauge and the arch encased in a tubular system that provides electronic isolation and permits the adjustment of the distance between the feet (fig. 1)*. The arch can be statically calibrated in grams by suspending a known weight across the feet of the arch. Shimosato and his colleagues [23] have reported that the encased arch has a uniform frequency response to 45 Hz which is adequate for recording CF at heart rates up to 240 beat min⁻¹.

Attachment and orientation of the arch. The methods presented here apply to the dog heart; however, small animal arches are available for use in cats, rabbits and rats. In dogs, the SGA can be sutured to either the left or the right ventricle. On the anterior wall of the right heart, two double

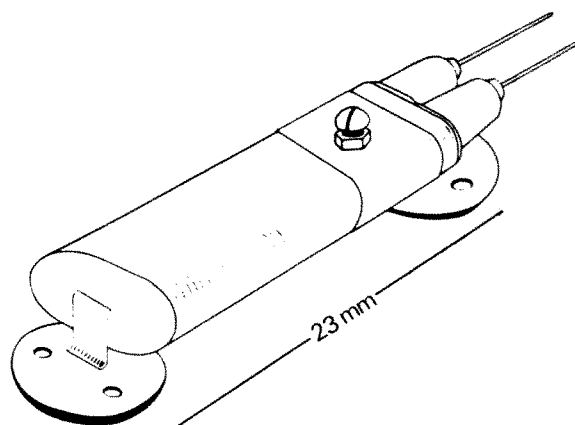


FIG. 1. A metal-encased arch with movable foot. This protection has been found necessary for use in chronic experiments since ordinary insulating plastics break down in body fluids. The casing permits adjustment of the length between the points of attachment, and lead wires are taken out through tiny stuffing boxes at the end of the casing.

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*Walton-Brodie strain gauge arches are currently produced by Warren Research Products, P.O. Box 412, Charleston, South Carolina 29402, U.S.A.

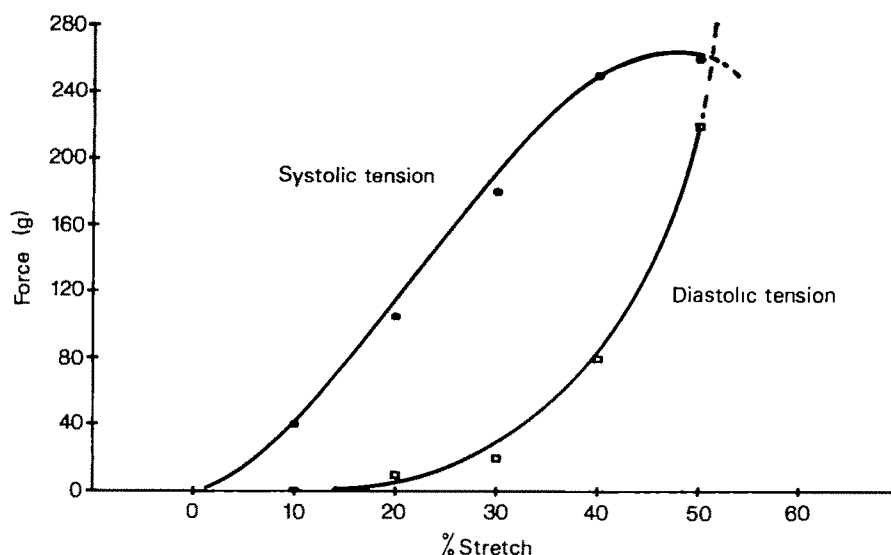


FIG. 2. This figure illustrates the Starling effect generated by stretching the muscle subtended by the feet of the strain gauge arch. In this case the strain gauge arch was calibrated in grams and the initial muscle beneath the feet was 20 mm. The muscle segment was then stretched in 2-mm increments and CF recorded. Systolic tension is the amplitude of CF excursion in grams and diastolic tension is the difference between baseline tension (zero) and CF during diastole. It has been our experience that curves generated from these measurements will cross (dashed lines) at or near the peak of the Starling curve.

sutures are placed approximately 2 cm apart and parallel to the base of the heart. The suture areas and the area between the sutures should be relatively free of coronary arteries. For best performance, the sutures should penetrate the ventricular wall completely. With the feet of the SGA set 2 cm apart, the sutures are threaded through the holes of the feet and snugly tied. The suture material should be large in order to avoid tearing of the muscle (we prefer cotton thread for acute experiments). Placement of the SGA on the left heart is accomplished in a similar manner with the following exceptions: the SGA should be positioned perpendicular to the anterior descending coronary artery, and suture depth should be approximately 75% of the thickness of the ventricular wall. Suture depth influences SGA recording quantitatively, but not qualitatively [9]. With the SGA in place, the muscle segment subtended by the feet of the SGA is stretched approximately 40% by separating the feet of the SGA. This manoeuvre places the muscle segment at or near the peak of the Frank-Starling curve. In fact, a Frank-Starling curve can be plotted with data obtained by separating the feet of the SGA in 1-mm increments (fig. 2). After the muscle is stretched the preparation should be allowed to

stabilize for approximately 30 min, during which time the diastolic tension will decrease as a result of relaxation of the slow elastic elements in the heart.

CONDITIONS ALTERING CONTRACTILE FORCE RECORDINGS OBTAINED WITH THE WALTON-BRODIE STRAIN GAUGE ARCH

Afterload

Afterload, defined as aortic pressures, has little influence on strain gauge arch performance [22]. However, changes in CF observed following an increase in aortic pressure were shown by Robie and Newman to be caused by increases in ventricular end-diastolic pressure which in turn effected an increase in ventricular wall mural force [22]. These investigators found it technically difficult to separate afterload and preload changes which may account for the inconsistent changes in SGA recordings following changes in afterload.

Their study appears to indicate that decreases in CF associated with increases in aortic pressure actually resulted from increases in preload. On the other hand, if afterload is defined as ventricular systolic mural force, then a linear relationship exists between increases in systolic mural force

and decreases in CF measured with the strain gauge arch. If an increase in afterload systolic mural force could be produced without an increase in preload, CF would decrease. This relationship is described by the equation $\% \Delta CF = 99.9 - 2.91(\Delta SMF)$ where $\% \Delta CF = \%$ changes in CF and $\Delta SMF =$ the change in systolic mural force [22]. It should be pointed out that the preceding discussion is valid only if the interventions or agents used to alter afterload are devoid of inotropic activity and without effect on preload.

Preload

Increases in preload produce consistent and predictable decreases in CF recordings regardless of SGA orientation [22]. Increased ventricular pressure increases ventricular radius, thereby stretching the muscle to produce a Starling effect in the ventricle as a whole. The resultant changes in SGA recordings may occur as a result of increased muscle forces and elastic properties adjacent to the segment of muscle subtended by the feet of the SGA. Doubling ventricular diastolic pressure will reduce recorded CF approximately 10% [22].

Left ventricular end-diastolic pressure (LVEDP) and diastolic mural force (DMF) are comparable indices of preload [22]. An increase in either of these indices results in a decreased CF as measured with an SGA. If LVEDP increases, the heart compensates by increasing ventricular radius and diastolic mural force is thereby increased. (LaPlace relationship states that wall force is proportional to the product of pressure and the square of the radius.) Thus it follows that an increase in preload (diastolic mural force) will increase systolic mural force (afterload) with a consequent decreased CF as noted above. The relationship between preload and CF can be accounted for by equations appropriate for either LVEDP or diastolic mural force [22].

It is important to recognize the direction of change in CF that is dependent upon increases or decreases in preload or afterload. Agents devoid of inotropic activity will produce alteration in CF as described below. Vasoactive agents having positive inotropic activity may have part of their enhanced CF masked as a result of increased ventricular loads. The following discussion concerns the influence of preload and afterload on CF measured with the strain gauge arch positioned perpendicular to the anterior descending coronary

artery. Positioning of the arch may account for the difference in results reported by Cotten and Bay [9] and Robie and Newman [22] regarding the influence of ventricular loading on strain gauge arch recordings. The decrease in CF associated with increased ventricular load is believed to result from increased fibre lengths that resulted from increased load. The fibres subtended by the feet of the arch are normally stretched 50%. These fibres are not isolated and, in fact, account for only part of the measured CF. Fibres adjacent and parallel to fibres beneath the feet of the arch are stretched to some degree and contribute to the recorded CF. When the ventricle as a whole is stretched by increasing LVEDP, the forces in fibres adjacent to the arch which were tending to approximate the feet of the strain gauge arch would be decreased and result in decreases in CF as recorded by the strain gauge arch.

Heart rate

The Bowditch phenomenon or force-frequency relationship has been studied extensively since it was first described in 1871. Blinks and Koch-Weser have reported on the effects of this phenomenon in a variety of mammalian hearts [4]. In the dog heart CF recorded with the strain gauge arch increases with increasing heart rate over the range 60–180 beat min^{-1} (fig. 3). One

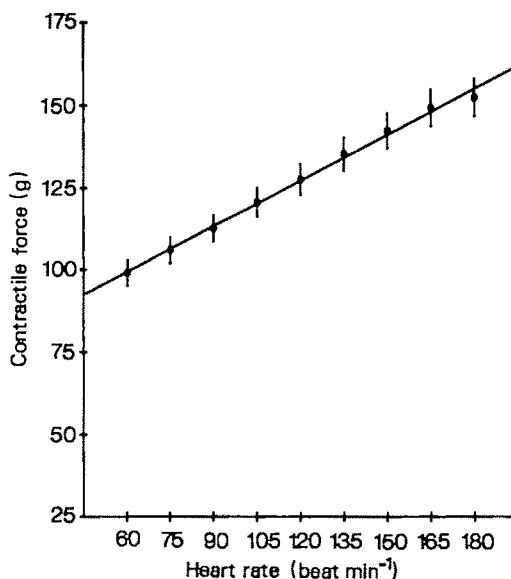


FIG. 3. Influence of heart rate on myocardial CF. Each point is the mean $\pm$ SEM of 72 experiments in dogs with complete heart block. CF stabilized within 2 min following a change in heart rate.

can anticipate a 50% increase in CF over the range 60–180 beat min^{-1} . Others have failed to observe a similar relationship between CF and heart rate in dogs [8] and in patients [24]. Cotten [8] reported a meagre 10% increase in CF associated with “substantial” increases in heart rate. While we cannot explain the differences in results between these observations, there is evidence that indicates that different barbiturates have different influences on the force–frequency relationship (FFR) [13]. The failure to observe a substantial FFR in patients [24] may reside in the fact that the patients were receiving digitalis and halothane. In our hands, digitalis tends to abolish the FFR by enhancing CF at lower heart rates more than at higher heart rates. Halothane depresses CF more at higher heart rates than at lower heart rates. We would anticipate that the combination of digitalis and halothane would abolish the FFR. The FFR should be kept in mind when studying agents with significant chronotropic actions. On the other hand, the FFR can be advantageous when studying agents the actions of which are rate dependent. For example, verapamil, which has a rate-dependent action, will completely abolish the force–frequency relationship.

Validity

A very large number of methods of estimating myocardial contractility have been developed. A good correlation exists between results obtained with the strain gauge arch and the ballistocardiogram in dog and man [11, 12, 26]. There appears to be a good correlation between CF recorded with the strain gauge arch and the first derivative of ventricular pressure, dP/dt [20, 25]. In fact, strain gauge arch recordings have been used to substantiate the validity of dP/dt observations [25]. Changes in LV dP/dt and CF were found to parallel each other in dogs made ischaemic [3]. Unfortunately, the strain gauge arch method has not been systematically compared with other popular methods of myocardial contractility measurement. We cannot explain this, since there have been hundreds of scientific publications using the strain gauge arch [29]. Despite the paucity of validity studies, use of the strain gauge arch is still frequently described in scientific publications and the data from its use are consistent with other measurement techniques, which confirm our opinion that the strain gauge arch is a useful measure of myocardial contractile function. An example of its use to

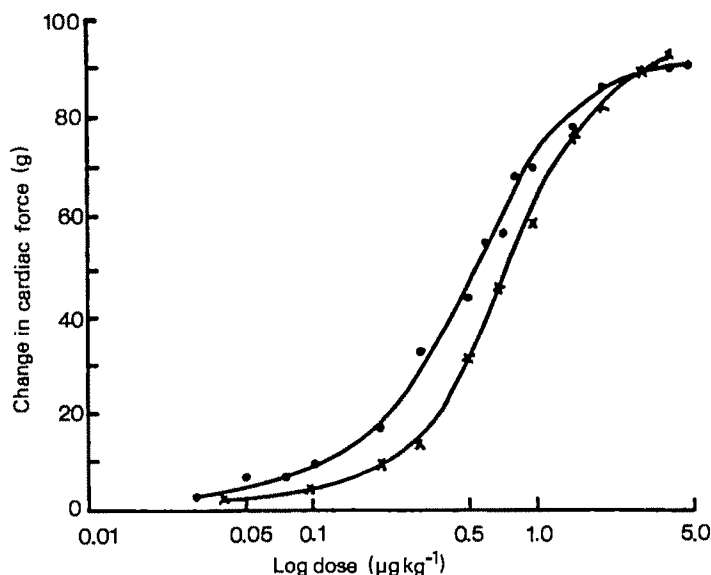


Fig. 4. Representative dose-response curves for the effects of 1-adrenaline (●) and 1-noradrenaline (x) on the force of ventricular contraction. Each change in contractile force was calculated from the control immediately preceding the injection. These data were taken from a typical experiment with an anaesthetized and vagotomized open-chest dog. Similar dose-response curves were obtained with these two amines in the unanaesthetized and unpremedicated dogs.

demonstrate the dose-effect relationship of adrenaline and noradrenaline is given in figure 4 [10]. Finally, it should be kept in mind that, although the recordings from the strain gauge arch are obtained from a segment of muscle contracting isometrically, CF recorded is actually a predictor of the force that would be generated by the whole ventricle contracting isometrically.

Limitations

The usefulness of chronically implanted strain gauge arch seldom exceeds 7–10 days. Best results are obtained from acute investigations in which substantial changes in heart size do not occur [9, 22].

Large variations in temperature (10 °C) result in baseline shifts and slight changes in amplitude of contractions [23]. Use of the strain gauge arch on the right ventricle has not received as thorough analysis as use on the left ventricle; however, in some circumstances right ventricular studies may provide more meaningful information than left ventricle studies, because afterload is usually less altered [22].

USE IN ANAESTHETIC RESEARCH

Despite the fact that the strain gauge arch is a highly invasive measurement, it has been used often in anaesthetic research in animals and even in man. Most has been in the dog, with investigations approximately evenly divided between acute and chronic procedures.

Inhalation anaesthetics

Ether, chloroform, cyclopropane and divinyl ether were studied in a chronic canine preparation [6]. In this early study of the effects of anaesthesia on CF it was found that all four of these inhalation anaesthetics produced dose-related decrements in right heart myocardial CF. It was observed in these chronic dogs that with induction during the early excitement stage (stages I and II) there was an increase in contractile force. Interestingly, it was noted with cyclopropane that, despite maintenance of heart rate and arterial pressure, there was a decrease in CF. This dichotomy between circulatory variables, heart rate and arterial pressure *v.* CF, has been found also with ketamine.

The cardiovascular effects of halothane have probably been as well studied as any anaesthetic drug. The strain gauge arch has been used in the

dog [16, 18] and man [5, 16, 17]. In 1961 there were independent reports from two institutions showing that the "new" inhalation anaesthetic, halothane, produced decreases in myocardial CF [5, 16, 17]. The most thorough study was by Mahaffey's group [16], who showed that halothane produced dose-related decreases in CF and that these changes were *direct*. They were independent of perfusion pressure and changes in the autonomic nervous system [16]. This paper was also the first to show a direct link between halothane CNS depression (EEG changes) and myocardial contractile force. In two clinical reports circulatory depression associated with halothane was found to be at least in part the result of direct negative inotropic effects [5, 17]. Furthermore, these effects were dose related and not influenced by type of heart disease or the presence of digitalis. In a more recent study in dogs, halothane was found to produce smaller decrements than enflurane at equi-MAC doses (fig. 5) [18]. This finding supports the generally held clinical impression that enflurane has greater negative inotropic effects than either halothane or isoflurane. The decreases in myocardial CF produced by methoxyflurane are similar to those of halothane [1] and are related to blood concentrations of methoxyflurane [2].

I.v. anaesthesia

Drugs administered *i.v.* during anaesthesia consist of anaesthetics and neuromuscular blocking agents. Both have been studied with the strain gauge arch. In separate investigations, Longnecker [14, 15] has compared the direct effects of tubocurarine and gallamine on right ventricular CF. In patients during cardiopulmonary bypass, tubocurarine 0.4 mg kg⁻¹ significantly reduced the perfusion pressure, but had minimal effect on CF [14]. In a similar study, gallamine 2.6 mg kg⁻¹ seemed to increase perfusion pressure and in some patients (three of five) there was an increase in CF [15]. These studies clearly differentiated the cardiovascular effects of the two drugs, illustrating that drugs given for one primary purpose (neuromuscular blockade) could have very different cardiovascular effects.

The effects of pentobarbitone 25 µg kg⁻¹ on myocardial contractility were demonstrated by Newman and Pruett in 1972 [19]. Pentobarbitone produced significant negative inotropic effects, but the depression was not prolonged,

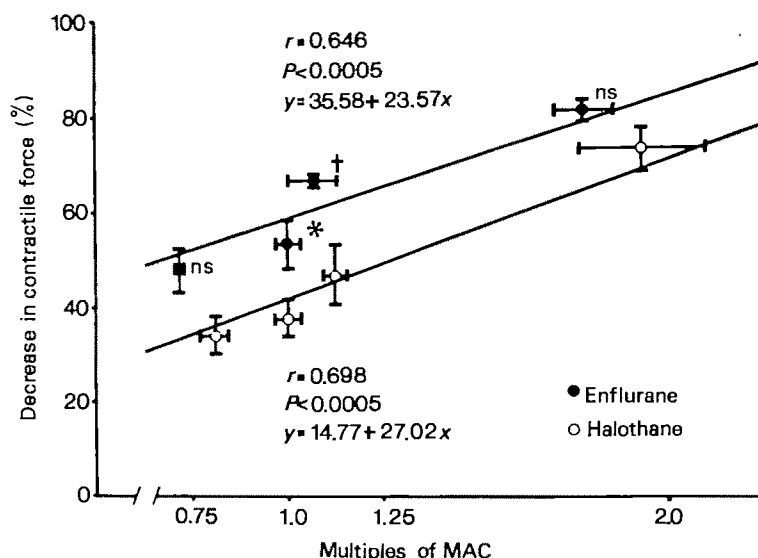


FIG. 5. The effects of end-tidal concentrations of enflurane and halothane (expressed as multiples of MAC) on right ventricular contractile force expressed as per cent decrease from control. Each point represents mean values from six animals $\pm$ SEM. Repeated measures analysis of variance indicated that the pattern of depression produced by enflurane was significantly greater than the pattern of depression produced by halothane ($P < 0.01$). All values are significantly different from control ($P < 0.05$). ns = Not significantly different from halothane response; *significantly different from halothane response ($P < 0.05$); †significantly different from halothane response ($P < 0.025$).

lasting less than 40 min. The implications of this study are that pentobarbitone, which is widely used as a basal anaesthetic in the laboratory, can be used without concern for myocardial depression after 40 min. Ketamine, like cyclopropane, has disparate effects on the circulatory variables heart rate and arterial pressure compared with CF [27]. There is a dose related, but transient (lasting less than 30 min) decrease in CF after ketamine. The clinical implication of this is that myocardial depression may occur despite apparent normal or even increased heart rate and arterial pressure.

Although ethanol is not generally considered nor routinely used as an anaesthetic, it is a ubiquitous drug found often in traumatized patients. Ethanol has been shown to decrease significantly the CF of the dog left ventricle [21]. Furthermore, the presence of ethyl alcohol further decreases CF that occurs with haemorrhage. The clinical implications of these findings are that anaesthetic drugs with their own negative inotropic effects may be additively depressant in ethanol intoxicated patients, particularly those who are hypovolaemic.

SUMMARY

The Walton-Brodie strain gauge arch is an instrument that quantitatively measures CF. Like many methods, the strain gauge arch is affected by loading conditions and heart rate. Nevertheless, this methodology, when properly used, has proved very useful in describing the direct action of anaesthetic drugs. Knowledge from strain gauge arch use has stimulated research to explain the negative inotropic effect of anaesthetics and helped clinicians understand the cardiovascular effects of drugs that they may wish to use.

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RELIABILITY OF PCWP AS AN INDEX FOR LEFT VENTRICULAR PRELOAD

H. VAN AKEN AND E. VANDERMEERSCH

WHAT IS PRELOAD?

Preload is classically derived from the measurement of end-diastolic fibre length. Each step away from end-diastolic fibre length creates problems.

In substituting end-diastolic volume for fibre length, we assume that the ventricle is a thin-walled sphere, when in fact it is a much more complex structure [2, 7]. Thus when diastolic volume of the ventricle is increased, fibre length is increased, but not to a uniform degree in all parts of the ventricle, because the left ventricle has been shown to be both structurally and functionally non-homogenous.

Because of logistical problems in obtaining a ventricular volume, pressure measurements have been substituted. However, in substituting end-diastolic pressure for fibre length, we must additionally assume that there is a known relation-

ship between pressure and volume. This relationship is not defined, for two reasons. First, the pressure–volume relationship of the left ventricle is curvilinear. Second, the working conditions in terms of the Frank–Starling mechanism change drastically with changes in ventricular distensibility. The same left ventricular end-diastolic pressure (LVEDP) may indicate a high volume when a ventricle has a normal compliance and a low volume when a ventricle has a decreased compliance (fig. 1). The end-diastolic volume is determined by ventricular distensibility (compliance) and the pressure acting to distend the ventricle—the transmural pressure (P_{tm}). The transmural pressure is the difference between LVEDP and the juxtacardiac pressure. A non-compliant ventricle or one surrounded by an increased intrathoracic pressure, requires a higher

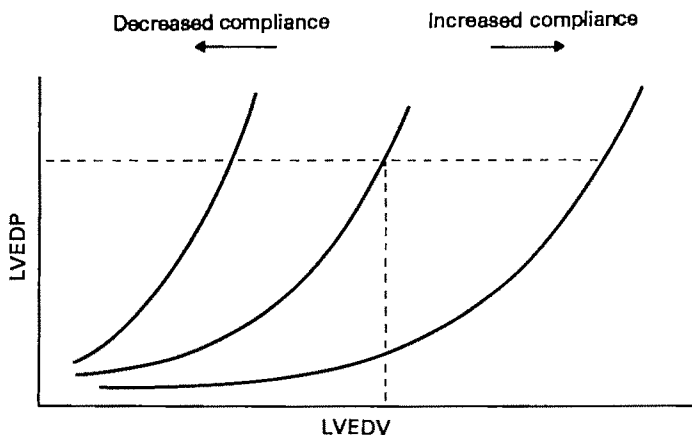


FIG. 1. Influence of change of ventricular compliance on left ventricular end-diastolic pressure (LVEDP) and left ventricular end-diastolic volume (LVEDV).

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than normal intracavity pressure to achieve any specified presystolic volume. Figure 2 gives three alternative interpretations of an increased left

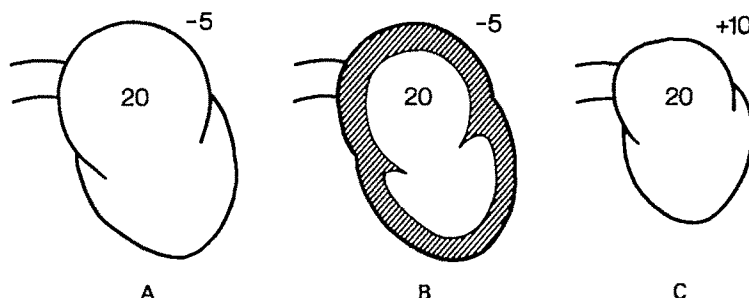


FIG. 2. Three alternative interpretations of an increased left ventricular end-diastolic pressure (LVEDP) (see text for detailed explanation).



FIG. 3. Pressure-volume relationship of the left ventricle.

ventricular end-diastolic pressure: an increased distension of a normally compliant ventricle and a normal juxtacardiac pressure (A); a normal or diminished end-diastolic volume (preload) of a non-compliant ventricle (B); and a normal or diminished end-diastolic ventricular volume (preload) with a high juxtacardiac pressure (C).

Changes in volume of the left ventricle at end-diastole may produce different changes in pressure depending on the location on the pressure-volume curve (fig. 3). At a low ventricular preload, a large increase in end-diastolic volume will be accompanied by only a small increase in end-diastolic pressure. On the other hand, at high ventricular preload (high end-diastolic volume) a small change in the end-diastolic volume will be associated with a large variation in end-diastolic pressure.

In practice, left ventricular end-diastolic pressure can be used to estimate left-ventricular end-diastolic volume only when good approximations of ventricular compliance and juxtacardiac pressures are available. However, juxtacardiac pressure is often difficult to estimate accurately and the ventricular pressure-volume relationship can vary abruptly in response to ischaemia, oncotic changes and changes in temperature [8]. Opinions

are still divided about drug induced changes in compliance [4, 5]. Therefore, an increase in the left ventricular end-diastolic pressure may not necessarily signify failure and dilatation of the ventricle, and a normal pressure may not indicate that all is well. Thus the measurement of end-diastolic pressure may not provide an accurate method of determining the preload of the ventricle [9].

Changes in left ventricular compliance may affect stroke volume. Figure 4A (A→B) shows a sudden decrease in stroke volume associated with no change in PCWP which, usually, will be interpreted as being the result of decreased myocardial contractility. However, if the ventricle becomes less compliant there may be, for the same PCWP, a decrease in LVEDV (fig. 4B: A→B). Thus the decrease in stroke volume could be the result of a decreased preload (fig. 4C: A→B) instead of a decreased contractility.

The treatment indicated, as long as PCWP is low and pulmonary oedema is not a problem, is to increase preload by volume infusion or reduce left ventricular afterload (and so increase compliance), instead of increasing contractility with inotropes. It is apparent, therefore, that PCWP may not be a reliable indicator of LV preload. In clinical practice it is essential to assess the patient's response to therapy in order to optimize treatment.

INTERPRETATION OF PULMONARY ARTERY WEDGE PRESSURE MEASUREMENTS

It is generally assumed that, under most circumstances, PCWP accurately reflects mean left atrial pressure. However, this assumption is correct only if the pulmonary vascular system distal to the catheter tip (that is the pulmonary capillaries and

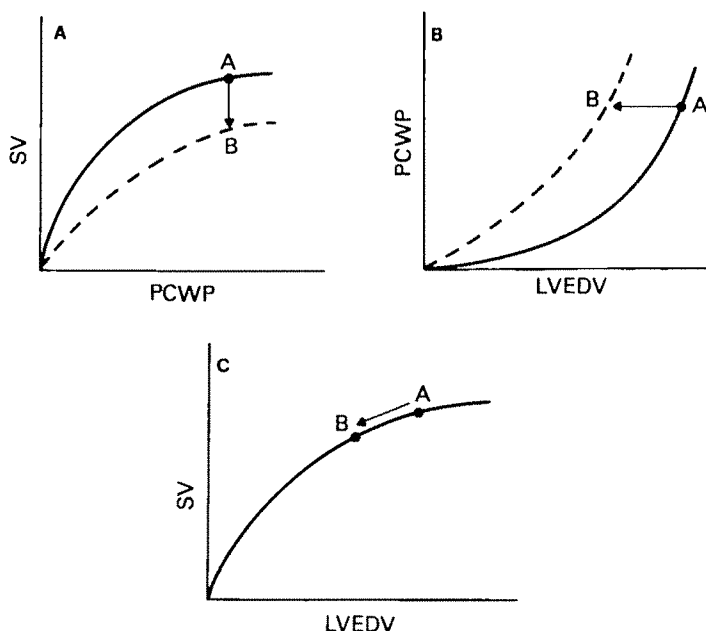


FIG. 4. Effects of changes in left ventricular compliance on stroke volume (SV), pulmonary capillary wedge pressure (PCWP), and left ventricle end-diastolic volume (LVEDV) [9].

veins) is freely patent and provides a direct, blood-filled vascular connection between the catheter tip and the left atrium, thus serving, in essence, as a direct extension of the catheter. If any interruption, whether anatomical or functional, occurs in this system, wedge pressure will no longer reflect mean left atrial pressure.

West and co-workers [13] demonstrated that there is a marked variation in blood flow existing within the human lung as a result of the interrelationships between the alveolar and vascular pressures (fig. 5). In the upper part of the lung (zone 1) the alveolar pressure exceeds both pulmonary arterial and venous pressure, with the

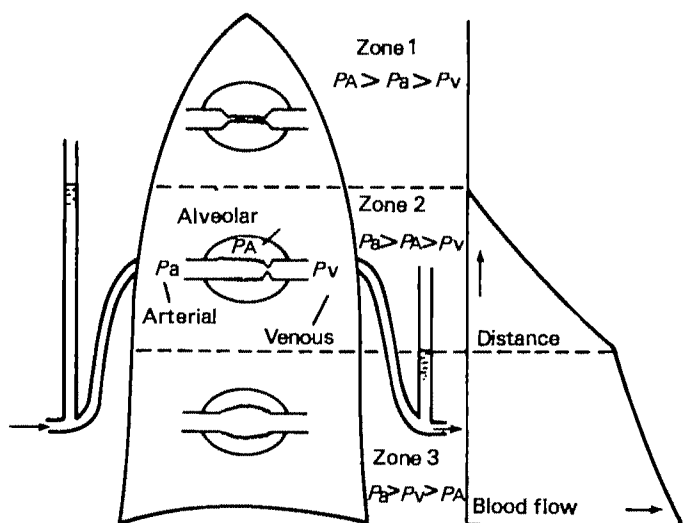


FIG. 5. Model of uneven distribution of blood flow in the lung based on the pressures affecting the capillaries [13].

result that pulmonary capillaries are usually closed and no blood flow occurs. This effectively precludes reflection of left atrial pressures. In the central areas of the lung (zone 2) flow is primarily determined by the balance between pulmonary arterial and alveolar pressures only, because in these zones, alveolar pressure commonly exceeds pulmonary venous pressure. Balloon inflation and catheter wedging will, in fact, convert a zone 2 situation to a zone 1 situation by preventing blood flow.

Thus, if the catheter is lodged in either zone 1 or zone 2, PCWP will not reflect mean left atrial pressure, but rather alveolar pressure. In the dependent part of the lung (zone 3) the capillaries remain open, because both pulmonary artery and venous pressures exceed alveolar pressure. As a result there is free communication between the left atrium and pulmonary arteries. Wedge pressure will reflect left atrial pressure accurately only when the catheter tip is in this zone.

Lateral chest x-rays, with the catheter in the wedge position, may be needed to ascertain that the catheter is positioned correctly below the left atrium [12]. Fortunately, most of the lung is in zone 3 when a patient is supine; flow-directed catheters will usually enter zone 3 because most blood is flowing to this area [6]. The incidence of placement in other zones is greater in patients with low vascular pressure resulting from hypovolaemia, or in those with increased intra-alveolar pressures (for example as might be developed during the use of PEEP). However, as long as the catheter tip remains below the left atrium, zone 3 conditions will exist, despite high PEEP. Thus wedge pressures can still provide reasonable accurate estimates of mean left atrial pressures.

VENTILATION AND PCWP

The positive and negative swings in intrathoracic pressures associated with all forms of ventilation influence intraluminal pulmonary vascular pressure. Because intrathoracic pressure is closest to atmospheric pressure during end-expiration, regardless of whether the patient is breathing spontaneously or with the help of mechanical ventilation, all pressures should be measured at this point of the cycle to minimize the influence of intrathoracic pressure swings [10].

Errors in the measurement of wedge pressure during PEEP may be caused by the increase in the alveolar pressure at end-expiration, which in-

creases the size of zones 1 and 2, especially in a hypovolaemic patient, and by the increase in pleural pressure associated with the increase in lung volume. This may decrease the effective transmural pressure (intraluminal pressure minus intrapleural pressure) because the increase in intraluminal pressure may be less than the increase in pleural pressure.

In any patient, the effect of PEEP on intrapleural pressure depends on that patient's lung compliance. Thus in a patient with decreased lung compliance in whom the effect on intrapleural pressure is minimal, intraluminal pressure reflects transmural pressure and actual filling pressure. However, in a patient with a normal or increased lung compliance, intrapleural pressure increases with PEEP and intraluminal pressure will no longer reflect true filling pressures.

The problem caused by PEEP cannot be overcome by measuring PCWP when PEEP is reduced or discontinued, since this would affect venous return and so create a completely different haemodynamic setting [11]. Theoretically it is better to measure transmural filling pressure, which is the difference between intravascular pressure and extravascular pressure (= pleural pressure). Pleural pressure can be measured directly [1] or by an intraoesophageal balloon [3], but this is difficult in clinical practice.

CONCLUSIONS

Many pathological conditions exist in which PCWP may not estimate left ventricular preload. Furthermore, there are many sources of error in the measurement. In view of these limitations it is vital to adopt a more critical attitude in evaluating data derived from the pulmonary artery catheters.

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IS THE MEASUREMENT OF CARDIAC OUTPUT USEFUL IN CLINICAL PRACTICE?

S. H. TAYLOR AND B. SILKE

The measurement of cardiac output is frequently undertaken without serious consideration of the principles involved and the technical limitations of the methods used. The principles involved in the Fick and indicator dilution methods are easy to understand but, because of their invasive nature, difficult to apply in practice. In contrast, many of the non-invasive methods involve complex principles and mathematical solutions, but are immensely more convenient to apply in patients. The prime consideration for the investigator is a clear understanding of the obligatory conditions, both theoretical and practical, that are essential for the correct application of the particular method of measurement he may select. It is intended that this review will serve two purposes: as a reminder of some of the different principles involved in the measurement of cardiac output and as a warning of the many potential pitfalls the unwary investigator may encounter in practice.

THE FICK METHOD

This method, the principle of which was enunciated by Fick in 1870, has probably been that most widely used for the measurement of cardiac output in man. Unfortunately, the reverence in which the method is held has elevated it to the "gold standard" against which to validate other methods of cardiac output measurement. This misplaced enthusiasm is a reflection of an uncritical approach to the practice of the principle.

The theory and application of the Fick principle are clear [3] (table I). It may be applied to the measurement of flow through any territory in which the concentration of the substrate being measured in the entrance and exit vessels is truly representative of that entering and exiting from all

sources. In its application in man to the measurement of cardiac output, or more exactly pulmonary blood flow, it is seen in its most advantageous circumstance. Blood flow through the lungs is determined by measuring oxygen content of blood from the pulmonary and systemic arteries simultaneously with determination of respired oxygen. Unfortunately, the conditions for meeting even these superficially simple and well defined requirements are less than ideal in clinical practice. Many of the theoretical conditions obligatory for the correct application of

TABLE I. *The Fick Principle*

Theory (Fick 1870):

$$dV/dt = Q_{out} C_{out} - Q_{in} C_{in}$$

where

$$dV/dt = \text{rate of uptake of } V$$

$$Q = \text{rate of blood flow}$$

$$C = \text{concentration of } V$$

Practice:

If integrated with respect to time

$$\text{If } Q_{out} = Q_{in}$$

$$Q(T) = VO_2 / (Ca_{O_2} - Cv_{O_2})$$

TABLE II. *The Fick Method. Theoretical conditions for application*

- (1) Volume of pulmonary capillaries constant
- (2) Rate of transfer of oxygen constant and homogeneous
- (3) Oxygen rapidly transferred and completely mixed
- (4) Blood sampling should be related to volume flow

TABLE III. *The Fick Method. Practical conditions for application*

- (1) Absolute equality between rate of oxygen uptake measured from inspired-expired air and transfer rate of oxygen transfer in pulmonary capillaries
- (2) SA_{O_2} and Pa_{O_2} must be constant
- (3) No significant changes in RV and LV outputs
- (4) No cardiac, pulmonary or hepatopulmonary shunts
- (5) Technical precision of blood and gas analysis

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TABLE IV. *Assessment of measurement errors in Fick cardiac output determinations*

Measurement	Observed value	Estimated maximum error	Estimated maximum error in calculation of cardiac output	
			Percentage error	Absolute error (at cardiac output of 6 litre min ⁻¹) (litre min ⁻¹)
Spirometric measurements	25 cm	0.1 cm	< 1	0.02
Barometric pressure	760 mm Hg	1 mm Hg	< 1	0.01
Spirometer temperature	20 °C	0.2 °C	< 1	< 0.01
Time of collection	4 min	5 s	2	0.12
Oxygen extraction	3 %	0.1 %	3	0.2
Blood oxygen carrying capacity	20 vol %	1 vol %	5	0.3
Blood oxygen saturation	95 %	2 %	5	0.3
	40–80 %	2–7 %	10	0.6

the principle are difficult, if not impossible to validate (table II).

In practice, the essential conditions for measurement of the cardiac output by this principle are equally difficult to achieve (table III). They may be partially satisfied under strict laboratory scrutiny, but extreme vigilance is required. This is illustrated by consideration of the particular errors involved and their *minimal* magnitude (table IV). However, if such critical attention is applied to the measurement, then its variability can at least be reduced to reasonable proportions. This is the crucial factor in considering its clinical utility. Although complete satisfaction of the

theoretical and practical principles involved should remove any major systematic error in the measurement, this is not of the same importance in clinical practice as reduction in the variability of the measurement. If the Fick method is applied under the best possible laboratory and "clinical" circumstances, then the variability of the measurement may be reduced to an acceptable level (fig. 1).

Practised under the most ideal conditions, successive estimates of the cardiac output measured by the direct oxygen Fick method differing by more than 4 % at rest are attributable to factors other than the method of measurement at a confidence level of 95 % probability. This value probably indicates the ultimate precision that can be achieved with the technique in man under routine laboratory conditions.

Two points are worthy of emphasis. The conditions under which such admirably small variability was achieved were far removed from those obtaining in clinical practice. Reduction in variability of the method can be achieved only by constant attention, not only to the technical factors involved, but also to the physiological state of the subject under study. Wide and rapid changes in the cardiac output cannot validly be expected to be measured by this technique. Thus the maximum validity of the Fick method is achieved when blood flow across the lungs and oxygen transfer to the pulmonary capillary blood are constant. This is, of course, rarely if ever achieved in practice, and the further the conditions deviate from these ideal circumstances, the more the method is in

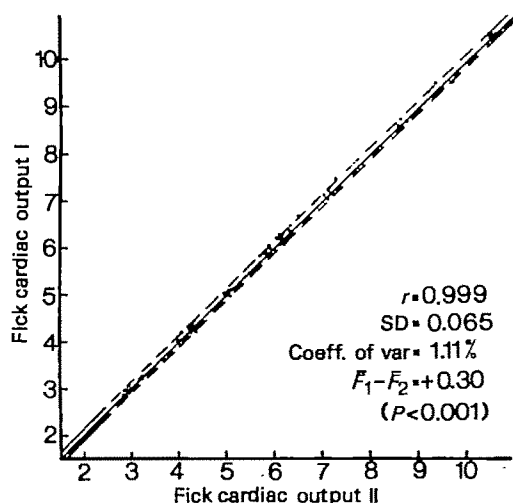


FIG. 1. Comparison of 84 consecutive Fick cardiac outputs at rest in 21 normal subjects.

TABLE V. *The indicator dilution method*

Theory:	$M_{\text{ind}} = Q \int_0^{\infty} C(t) dt$
Practice:	$Q = \frac{M_{\text{ind}}}{\Sigma C_{\text{ind}}}$

TABLE VI. *The indicator dilution method. Theoretical conditions for application*

(1)	Injection instantaneous
(2)	Volume of indicator small
(3)	Indicator rapidly and completely mixed
(4)	No loss of indicator in transit
(5)	Single channel at some part of system
(6)	Uniformity of volume flow
(7)	No change in volume
(8)	Constant distribution of indicator traversal times
(9)	Distribution of traversal times must be equal for indicator and blood
(10)	Sample curve must be representative
(11)	Sampled curve contains no recirculation
(12)	Sampling methods must not introduce concentration distortion or time-smearing

error. Thus in practical terms the method is at its most precise in man in measuring pulmonary blood flow in the normal subject at rest. When the technique is applied in conditions of a rapidly changing physiological state, as may occur under anaesthesia, then the method becomes open to serious potential errors and may give rise to entirely misleading information.

THE INDICATOR DILUTION METHOD

The principle underlying the indicator dilution method of measurement of the cardiac output is but an extension of the Fick principle (table V). Again there are a number of stringent theoretical (table VI) and practical (table VII) considerations that must be satisfied for the successful application of this method. As with the application of the Fick method, the utilization of the indicator dilution principle to measure cardiac output also involves a number of potentially substantial errors when it is applied in practice (table VIII). As with the Fick method, appreciation of the source of these errors and attention to minimizing them in practice allows the variability of the method to be reduced to reasonable proportions (fig. 2).

Exactly the same limitations apply to the application of the indicator dilution principle in

TABLE VII. *The indicator dilution method. Practical criteria for application*

- (1) Circulatory stability of the subject
- (2) Constant injection/sampling sites
- (3) Rapid injection of small amount of indicator
- (4) Precise knowledge of mass of indicator injected
- (5) Rapid and precise sampling/transcribing system
- (6) Accurate calibration method

TABLE VIII. *Assessment of errors in dye cardiac output method*

(1)	Error of measurement of injectate	< 1%
(2)	Error from dye curve distortion	< 2%
(3)	Error from alinearity of photocell	< 1%
(4)	Error from alinearity of recorder	< 1%
(5)	Error from build up in base-line dye level	< 2%
(6)	Error from calibration	< 5%
(7)	Error from failure to plot dye curve down-slope to infinity	< 2%
(8)	Observed error in measurements	< 1%

practice as apply to the Fick method in the same situation. Thus the maximum precision in measurement of cardiac output by indicator dilution obtains when the subject has a normal cardiac pumping function and is in a physiologically stable state. Under these conditions, when two consecutive dye curves are measured at the same heart rate then the measurement of cardiac

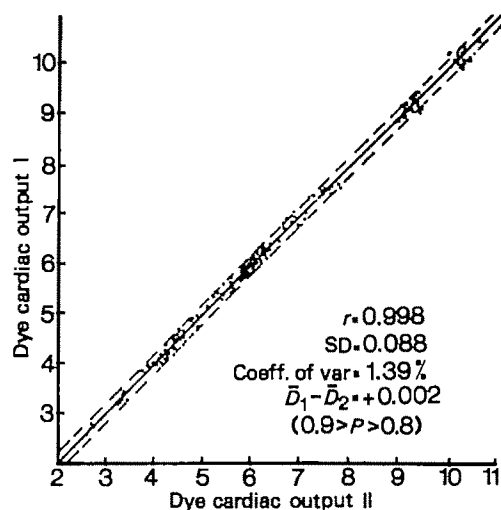


FIG. 2. Comparison of cardiac output measurements in subjects without heart disease made within 1 min and at the same heart rate. The coefficient of variation is expressed as a percentage of the mean value of all observations. The variance of the difference between the two values was homogeneously distributed (Bartlett's test: $P > 0.90$).

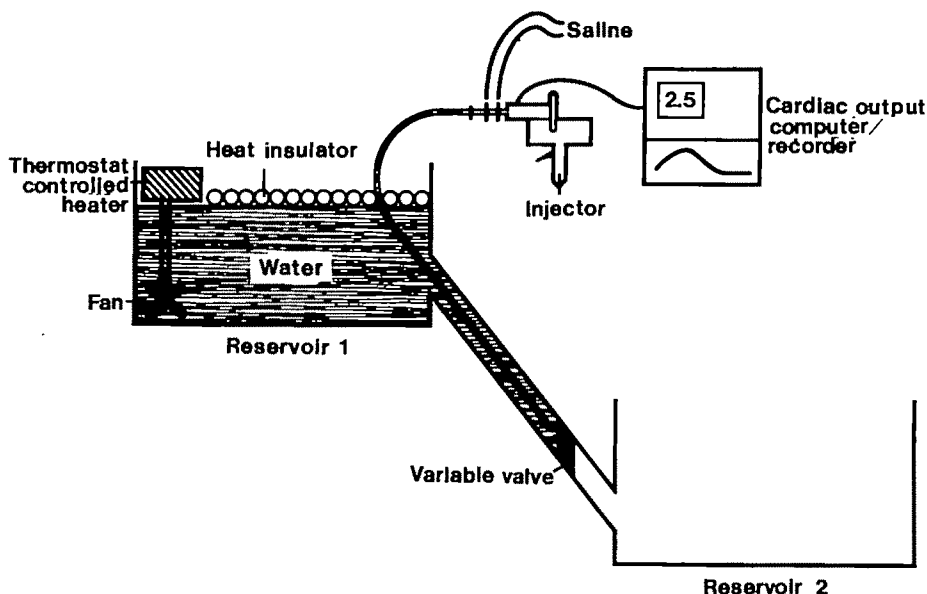


FIG. 3. The model for *in vitro* calibration used to determine the absolute validity of the thermodilution measurement of cardiac output.

output will differ by less than 6% in 95% of instances [3]. As with the Fick method, maximum errors are introduced by its application under rapidly changing physiological circumstances in patients with cardiovascular disease.

When first introduced, the indicator dilution method utilized colourimetrically detectable dye. This is immensely cumbersome in clinical practice involving, as it does, intra-arterial cannulation for the detection of the indicator; skin sensors are unreliable. It also involves tedious calibration of the system, which introduces its own difficult-to-measure errors. The introduction of cold water injection and down-stream sensing with sensitive thermocouples was a major advance in the potential clinical application of the method. However, thermodilution carries the common limitations, both in theory and practice, of all indicator dilution methods. In an attempt to establish the *absolute* validity of the technique (which has never been established for the dye dilution method) a simple model was developed to compare the absolute outflow of the system with that derived from the thermal indicator method (fig. 3). With very careful attention to such details as temperature of the fluid in the system (38 °C) and the cross-section of the outflow tube of diameter similar to the pulmonary artery, the method showed no systematic error (fig. 4).

A number of important practical details are obligatory, however, for the precision of the thermodilution method when it is applied in clinical practice. The site of injection must be constant so that the volume of blood to which the cold water injection is made is relatively constant; this can only be achieved if the catheter is firmly anchored. The saline at the point of injection must be at the externally monitored temperature;

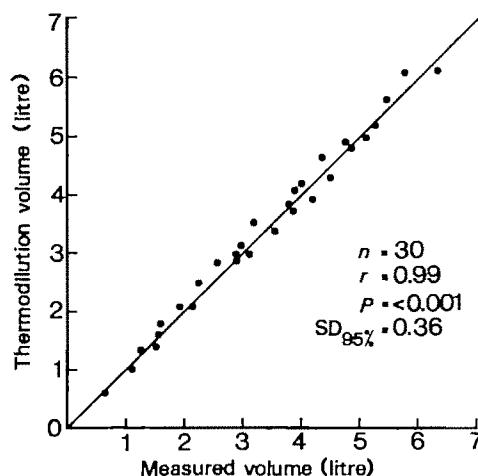


FIG. 4. Comparison of the thermodilution estimate and measured volume flow in the model.

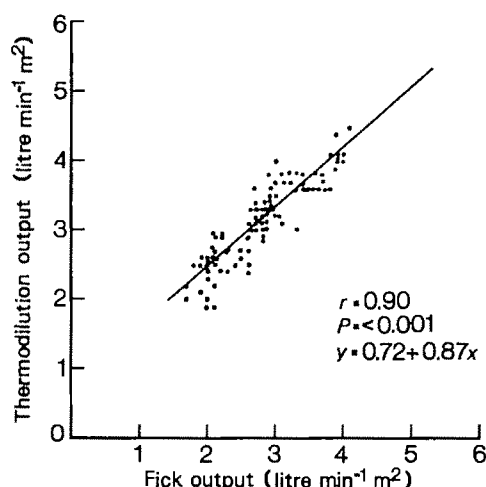


FIG. 5. Comparison of the Fick and thermidilution measurements of cardiac output at rest in 25 patients undergoing cardiac catheterization.

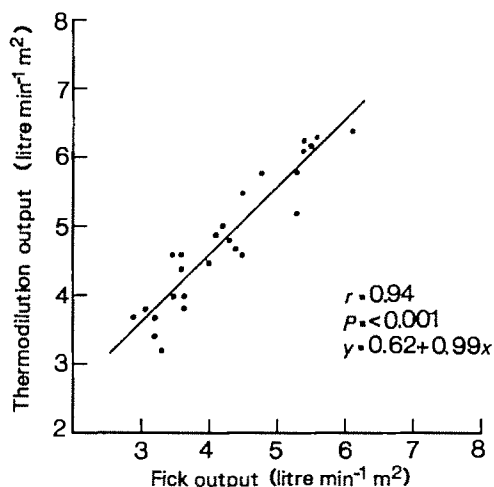


FIG. 6. Comparison of the Fick and thermidilution measurements of cardiac output during supine bicycle exercise in 25 patients undergoing cardiac catheterization.

this can be achieved only by repetitive flushing of the catheter by the injectate before the definitive injection is given. If the technique of thermidilution is compared with the Fick as practised under the close clinical scrutiny alluded to previously, then there is no major systematic error between the two techniques of measurement either at rest (fig. 5) or during dynamic exercise (fig. 6). If careful and constant attention is paid to these vital conditions of operation, and only then, the thermidilution method reveals a variability

TABLE IX. *Thermidilution variability*

Catheter laboratory (<i>n</i> = 12)	5.4% (2.3–9.3)
Coronary care unit	
Uncomplicated AMI (<i>n</i> = 20)	4.9% (1.6–12.1)
AMI + heart failure (<i>n</i> = 20)	6.1% (1.8–12.3)

under clinical conditions which places it amongst the most acceptable methods for the measurement of cardiac output by invasive techniques available at the present time. In practice the variability of thermidilution measurements may vary between 1.6 and 12.3% depending on the clinical situation (table IX).

COMPARISON OF FICK AND INDICATOR DILUTION METHODS OF MEASUREMENT OF CARDIAC OUTPUT

Comparison of the two methods has long been an uncritical interest of investigators. Neither can be satisfactorily validated in man. Both methods are also sensitive to the particular expertise of the laboratory and the clinical state of the patient under study. Each method contains inherent composite errors of the order of 5% which cannot be further reduced. Many comparisons have been reported, particularly between the Fick and dye dilution method of cardiac output (see review by Taylor [3]). The majority of reports have righteously claimed that there was no systematic discrepancy between the results of the two methods, but failed to emphasize the far more important fact that the variability between the two methods was unacceptably wide. In fact the variability was more than 25% in one-quarter of the results reviewed. This is to be expected when it is realized that the two methods involve totally different time constants. However, if this and all other factors are taken into account in the academic design of such a comparison, then a relatively close measure of agreement between the two methods emerges. If the study is conducted under similarly "ideal" conditions for each method, there is no systematic error and the variability between the two methods is small both at rest (fig. 7) and during steady state exercise (fig. 8). It should be emphasized, however, that such comparative exercises are relatively profitless and divert attention away from the details necessary to perfect the particular method it is intended to use.

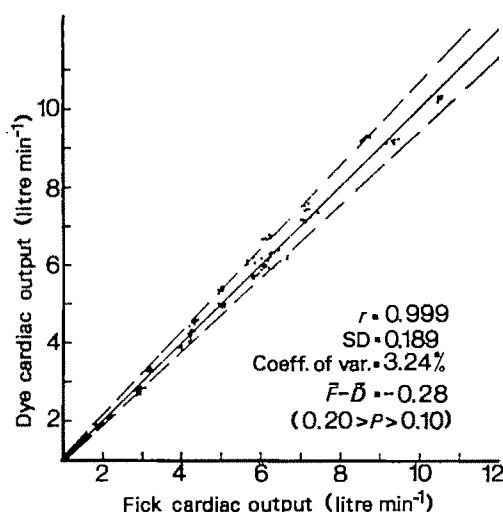


FIG. 7. Comparison of the Fick and dye cardiac output measurements in resting subjects without heart disease; five comparisons in each of 21 subjects. The interrupted lines are placed at 6.4% from the line of identity and refer to the 95% confidence limits calculated from the coefficient of variation. The variance was not homogeneously distributed (Bartlett's test: $P < 0.001$).

MEASUREMENT OF THE CARDIAC OUTPUT BY ULTRASOUND

Measurement of the cardiac output by methods utilizing invasive techniques has obvious limitations in clinical practice. Non-invasive methods have therefore been sought; amongst the most promising in terms of ease of application is the method using ultrasound determination of aortic blood flow.

The Doppler principle as applied to the calculation of flow relies on the following relationship:

$$fd = 2fo V \cos \theta / C$$

where fd = average Doppler frequency shift; fo = transmitted frequency; V = average velocity of red cells; θ = angle of insonation (angle between beam and centre-line axis of flow); C = velocity of sound in blood.

Using this relationship, the shift in Doppler frequency is proportional to the velocity of the moving blood cells. Even in laminar flow these cells move at different velocities, so fd consists of a wide frequency band. The intensity of a signal at any single frequency is proportional to the total number of cells moving at that velocity; the total intensity is proportional to the total number of moving cells.

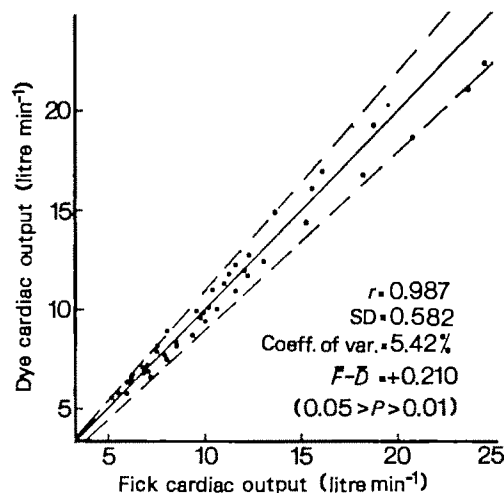


FIG. 8. Comparison of the Fick and dye cardiac output measurements during exercise in subjects without heart disease; two comparisons in each of 32 subjects. The interrupted lines are placed at 10.6% from the line of identity and refer to the 95% confidence limits calculated from the coefficient of variation. The small but significant bias between the Fick and dye values has been taken into account. The variance between the values was not homogeneously distributed (Bartlett's test: $P < 0.001$).

As certain constants (fo and C) are known, a simplified formula can be utilized:

$$V = \frac{fd}{k \cos \theta}$$

where k is a constant. Therefore, to determine the true average velocity of the moving cells requires knowledge of the angle θ (angle between the beam and centre-line of flow) and fd (the true average Doppler shift frequency).

Blood flow in the aorta can be estimated using Doppler ultrasound principles to calculate the average velocity of flow; provided the cross-sectional area is known, minute flow rate can then be calculated. Thus

$$Q = Vta \times CSA$$

where Q = flow rate ($\text{cm}^3 \text{ s}^{-1}$); Vta = true average velocity (cm s^{-1}); CSA = cross-sectional area (cm^2). However, a number of problems have restricted its application in clinical practice [1], particularly in acute situations. There are problems with accurate measurement of both aortic diameter and the true average velocity of blood flow. Previous methods have required an imaging system to measure the cross-sectional area of the aorta. In pragmatic terms, the vessel wall demarca-

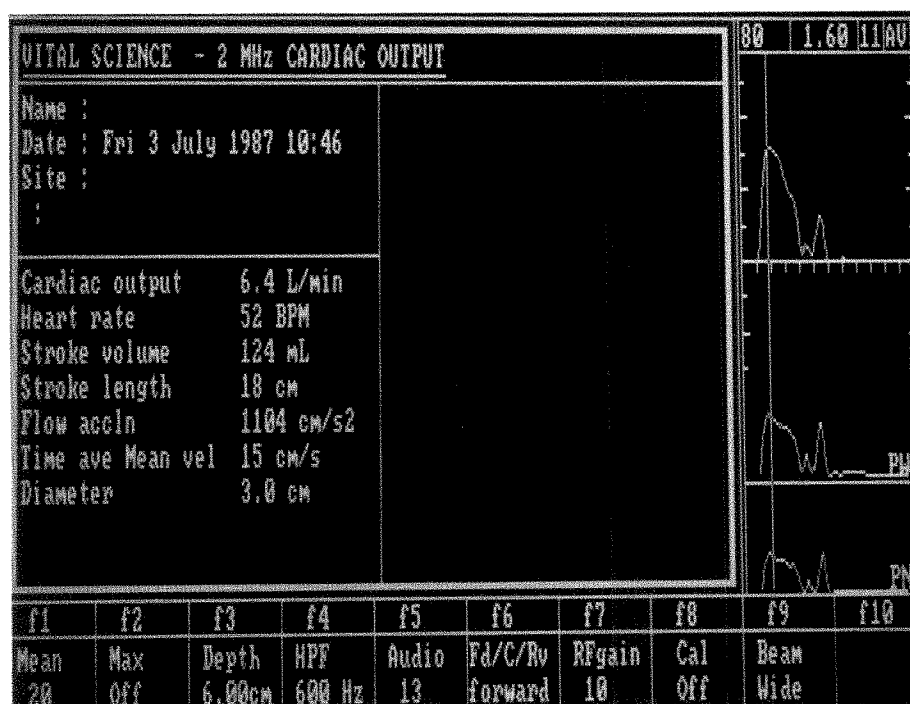


FIG. 9. Illustration of screen display of data derived by the Quantascope.

tion is often difficult to determine with precision and the consequent area calculation ($CSA = 3.14 \times \text{diameter}^2/4$), assuming a circular vessel, will tend to magnify any measured inaccuracy. It must be assumed that the anatomical cross-sectional area is the same as the flow lumen area.

The measurement of velocity of flow is also open to considerable errors. The ultrasound beam is small with respect to the vessel (on average < 10% of the cross-section) and therefore critically dependent on correct positioning. The angle of insonation is also difficult to estimate exactly and the major axis of flow may not be in the centre-line of the vessel. Thus the composite of these problems has led in clinical practice to variations in cardiac output estimates of $\pm 40\%$. This variability is clearly unacceptable for either dependable diagnostic or investigative exercises.

A new approach which circumvents many of these problems has been developed. The Quantascope [2-4] uses a suprasternal annular array transducer with two concentric ultrasound beams, one wide and one narrow. The wide beam (3 cm wide) uniformly encompasses the entire aorta, whereas the narrow beam samples the centre of

the vessel. In the wide beam, the intensity of each Doppler shift frequency is proportional to the number of cells moving at a specific velocity and the sum of all intensities is proportional to the total number of moving cells; thus the aortic cross-sectional area is proportional to the sum of all the individual Doppler shift frequencies (power of the Doppler shift signal). The power in the wide beam ($P_w = K_a$ (attenuation constant) $\times A_w$ (aortic flow lumen area)). Similarly, in the narrow beam $P_n = K_a \times A_n$ (flow lumen area of narrow beam). As $P_w/P_n = A_w/A_n$, then $A_w = A_n \cdot P_w/P_n$. Therefore, if A_n is precalibrated under conditions similar to human tissue, A_w (the aortic flow lumen area) is automatically computed from the ratio of the energy of the beams; when multiplied by the integrated velocity from the wide beam (estimating flow), an instantaneous computation of proximal aortic blood flow (i.e. cardiac output) is obtained (fig. 9).

The method used by the Quantascope is attenuation independent. It is not dependent on the angle of insonation under specified conditions. The aorta must lie within the wide beam, the narrow beam is within the blood vessel and the area of the narrow beam at any given depth is

known. The system is precalibrated using a Doppler phantom for the narrow beam, the wide beam power signal response is plotted and values initialized in the matched software. The correct operation at known flow rates is checked on a volume flow pump.

The accuracy and variability of this new echo-Doppler system has been assessed in a variety of clinical situations. In 21 coronary patients undergoing routine diagnostic catheterization before coronary artery bypass operation, eight to 10 thermodilution cardiac output measurements were compared with simultaneous Doppler determinations, over a 20-min period of *stable resting haemodynamics*. The average thermodilution and Doppler derived values were similar ($5.65 \text{ litre min}^{-1}$ and $5.5 \text{ litre min}^{-1}$, respectively; $n = 173$); the average difference was $0.14 \text{ litre min}^{-1}$ with an SD of the difference of $0.3 \text{ litre min}^{-1}$. The least squares relationship was $y = -0.28 + 1.02x$, with a correlation coefficient of 0.96 ($P < 0.001$) and a variance about the regression of $0.1 \text{ litre min}^{-1}$. The short-term variability of the Doppler technique was examined in 10 normal volunteers and in 25 patients with coronary artery disease. At 2-min intervals, eight to 10 consecutive estimates were obtained over a 20-min rest period. Consistently lower cardiac parameters were evident in the coronary patients (table X). In general, variability was similar for both groups (tending to be lower in normal individuals) and was $< 8\%$ for all variables. The average variability for cardiac stroke volume was 3.8% for the normal individuals and 4.4% for the subjects with coronary artery disease.

It should be emphasized that, although such reproducibility of values can be achieved with adequate training, the successful application of

the echo-Doppler device requires a not inconsiderable degree of skill. The positioning of the probe (in three planes) is critical; optimal results require the co-ordination of hand movement guided by complex Doppler visual and audible information. An average operator can expect to achieve technical competence having studied 50–100 subjects and perhaps over 6–8 weeks duration. Notwithstanding these operator requirements, our observations suggest that such Doppler techniques are accurate and reproducible, and are potentially applicable in a variety of acute clinical situations.

SUMMARY

The derivation of the "cardiac output" in man is fraught with difficulties whatever principle of measurement is used. The theories underlying the principles involved are sound; the problem arises in their application to the measurement in man. Of equal moment are the immense practical difficulties in applying the techniques available. Together these difficulties frequently give rise to unacceptable errors in the derivation of the "cardiac output". There is no "gold standard" of measurement; all methods have inherent difficulties in their application to man. If intense attention is paid to the practice of any one of the techniques available, then it is possible to reduce the variability of the measurement to acceptable proportions, but the conditions necessary to obtain such narrow ranges of variability in the human subject rarely obtain in routine clinical practice.

These realizations apply to the techniques available at present, and it is difficult to imagine that there will be further development of the invasive methods available which would negate these. In contrast, it is possible that refinement of some of the non-invasive techniques now being introduced will allow reasonably reliable measurement of the cardiac output with greater facility than is possible at present.

Finally, this brings into question the whole objective of the utility of measurement of cardiac output in practice. Frequently it is measured without due deference to its usefulness. Doubtless there are situations in which the measurement of cardiac output may be of scientific, if not of individual clinical benefit, for example the influence of drugs in hypertension and heart failure. However, these are specific circumstances that contrast markedly with the diagnostic utility of

TABLE X. *Quantascope parameters from normal volunteers and coronary patients (mean $\pm$ SEM). †Coefficient of variation—average percentage*

	Volunteers ($n = 10$)	Coronary patients ($n = 25$)
Cardiac output (litre min^{-1})	7.3 ± 0.4 (4.8)†	5.5 ± 0.15 (4.9)†
Heart rate (beat min^{-1})	59 ± 2 (3.4)	64 ± 2 (2.8)
Stroke volume (ml)	125 ± 8 (3.8)	87 ± 3 (4.4)
Stroke length (cm)	17.7 ± 1.1 (4.3)	12.4 ± 0.4 (5.4)
Flow acceleration (cm s^{-2})	1341 ± 85 (5.8)	773 ± 58 (7.4)
Time averaged mean velocity (cm s^{-1})	17.2 ± 0.9 (5.2)	13.0 ± 0.4 (5.6)

the measurement in clinical practice. In fact, the difficulty of making the measurement in these latter circumstances raises the reasonable question, is it really worthwhile?

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TRANSOESOPHAGEAL TWO-DIMENSIONAL ECHOCARDIOGRAPHIC EVALUATION OF ANAESTHETIC EFFECTS ON LEFT VENTRICULAR FUNCTION

M. K. CAHALAN, F. C. LURZ AND N. B. SCHILLER

Traditional methods of evaluating anaesthetic effects on left ventricular (LV) function have significant disadvantages. The assessment of pulmonary capillary wedge pressure provides only a limited indication of preload because of the complex relationship of LV diastolic pressure and volume, in addition to which, invasive haemodynamic monitoring is associated with potentially fatal complications. In contrast, two-dimensional transoesophageal echocardiography is potentially safer than invasive techniques and allows direct assessment of LV filling and ejection. It is thus an ideal technology for monitoring the effects of anaesthetics on LV function.

GENERAL THEORY AND TECHNIQUE

Piezoelectric crystals are the transmitters and receivers of the ultrasound waves used in echocardiography. The term "ultrasound" refers to any sound at frequencies above the level detectable by the human ear ($>20\,000$ Hz). Typically, these crystals send intermittent pulses of sound at 2.5–5 MHz and receive the reflected signal. When the ultrasound strikes an interface of different densities—for example that between the epicardium and blood—a portion of the ultrasound is reflected. By using multiple crystals (linear or phased array transducers) or rapidly moving a single crystal (mechanical transducer), multiple "sonar" images of the heart can be collated and displayed by an ultrasonograph as a two-dimensional tomographic image. Most ultrasonographs produce 30 such images per second. Viewed on a

monitor, these give the impression of a continuously moving, "real-time," cross section of the heart.

Modern ultrasonographs can measure the Doppler shift while simultaneously producing two-dimensional echocardiograms. The Doppler shift is the apparent change in frequency of an ultrasound wave when it is reflected from a moving object, for example, blood cells leaving the LV during systole. The change in frequency is proportional to the speed of the object. A point-by-point evaluation of the velocity of blood flow within the heart will quantify stroke volume and valvular function; however, the process is time-consuming. A recent refinement, colour-coded Doppler flow imaging, superimposes real-time colour maps of flow on two-dimensional echocardiographic images. Blood flow away from the transducer may be arbitrarily coded blue, flow toward the transducer may be red, and the differing velocities progressively "hotter" or "colder" shades of these colours. The viewer is presented with an instantaneous, albeit qualitative, image of intracardiac blood flow.

Although the basic principles and processing of transoesophageal and precordial (standard or routine transthoracic) echocardiography are identical, the former technique requires a modified transducer. At the University of California San Francisco, we use a commercially available 3.5-MHz oesophageal transducer system (Diasonics Incorporated, Ultrasound Division, Milpitas, California) consisting of 32 quartz elements mounted on the tip of a gastroscope (fig. 1). The fiberoptics of the gastroscope have been replaced by the wires from the transducer. The transducer is 35 mm long, 15 mm wide and 16 mm thick. Coupled to a commercially available ultrasonograph (Diasonics 3400, CV60, or CV6400), this system provides a 90° sector scan of an area 1–20 cm in front of the transducer.

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FIG. 1. Commercially available 3.5-MHz oesophageal transducer system (Diasonics, Incorporated, Cardioimaging, Milpitas, California). The distal tip of the modified gastroscope is shown in the magnified portion of the figure. Behind the light gray acoustical lens is the quartz ultrasound transducer.

After induction of anaesthesia and intubation of a patient's trachea, the transducer is inserted through the mouth and advanced into the oesophagus 35–40 cm from the incisors, providing a view of all cardiac chambers (fig. 2). The transducer is then advanced behind the left atrium, and the gastrosopic controls are used to lift the transducer behind the inferior wall of the LV to provide a short-axis cross-sectional view (fig. 3). Short-axis views can usually be obtained at multiple levels, including mitral valve, mid-papillary, and papillary base level. In approximately 8–10% of patients, the horizontal displacement of the heart by the contents of the abdomen prevents the papillary short-axis view. However, when available, these images can be recorded and analysed with a computer-assisted video system and can yield quantitative estimates of LV filling and ejection that are reproducible to within 10%. Although this analysis is too time-consuming for use in the operating room, it is easily accomplished in the research setting. In most patients, transoesophageal short-axis cross-sectional views are identical to precordial short-axis cross-sectional images. For precordial studies, the patient must be placed in the left lateral position, whereas left lateral or supine position (the usual position of

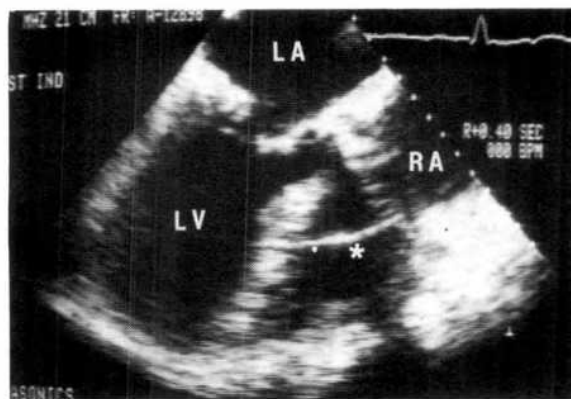


FIG. 2. A stop-action, four-chamber view of the heart. This image was produced with a transoesophageal transducer inserted 35 cm from the incisors. LV = left ventricle; LA = left atrium; RA = right atrium; the asterisk marks the image of the pulmonary artery catheter in the right ventricle.

anaesthetized patients) may be used for transoesophageal studies.

Echocardiography requires no ionizing radiation, and ultrasound has never adversely affected humans. At the University of California San Francisco, we have monitored more than 1000 patients using transoesophageal echocardiography, without complication, and we estimate that more than 5000 patients have undergone the

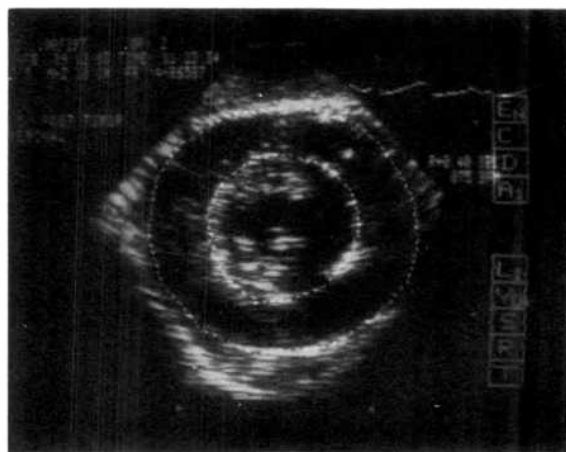


FIG. 3. A stop-action, short-axis echocardiogram of the left ventricle at end systole. The outlines of the images of the epicardium and endocardium have been traced by a video light pen system. A digital computer coupled to the light pen system estimates the cross-sectional area enclosed by these lines for calculation of systolic wall stress (see figure 4, p. 104, for orientation).

procedure at other institutions. One published report describes two patients who suffered temporary unilateral vocal cord paralysis after transoesophageal echocardiography was used during "sitting" craniotomies [4]. Both patients were positioned with nearly full neck flexion, and the recurrent laryngeal nerve was probably injured when the larynx, tracheal tube, and shaft of the gastroscope were compressed between the chin and vertebral column. These investigators now use a 5-mm gastroscope for patients positioned with extreme flexion of the neck, and have reported no further complications. Unless urgently required, we do not use transoesophageal echocardiography in patients who have a history of swallowing complaints, oesophageal disease or mediastinal radiation.

GLOBAL INDICES OF LV FUNCTION

Preload

LV preload is the stretch applied to the left ventricle as the blood distends it at end-diastole. If all other conditions remain unchanged, LV end-diastolic volume (LVEDV) correlates directly with stroke volume (the Frank-Starling effect) and can provide a reasonable assessment of preload. However, during anaesthesia, LVEDV is difficult to measure directly and thus preload is often derived indirectly by monitoring LV end-diastolic pressure (LVEDP) or pulmonary artery occlusion pressure (PAOP). Unfortunately, the relationship between LVEDV and LVEDP is not linear [8]. Moreover, in the presence of mitral valve dysfunction or changes in LV compliance, that relationship is unpredictable, and PAOP may not correlate with LVEDV. Transoesophageal echocardiography offers a practical solution to intraoperative preload assessment because, as with precordial echocardiography, it directly images the LV. Early studies demonstrated that two-dimensional echocardiography produces reliable estimates of LVEDV if an accurate geometric model of the LV is used and a sufficient number of different echocardiographic cross sections are evaluated [6, 20]. Typically, the heart is assumed to be shaped like a prolate ellipsoid. At end-diastole, LV length (L) is estimated from a long-axis cross section and LV area (A_c) from the short-axis cross section. LV volume (V) then equals $2/3(L)(A_c)$ [37]. More complex models are sometimes used, resulting in somewhat more

accurate estimates of LVEDV, when they incorporate many cross sections. However, echocardiographic estimates of LVEDV are consistently lower than angiographic estimates, probably because the former calculation excludes the volume of blood within the LV trabeculations.

Compared with precordial echocardiographic assessment of LVEDV, transoesophageal echocardiographic assessment is limited in one important way: LV length (L) cannot be estimated directly because the oesophageal transducer cannot be angled sufficiently to produce a true long-axis image. However, previous studies have shown that changes in A_c , rather than L , more directly reflect changes in LVEDV. A_c and LVEDV have been shown to have a linear relationship over a wide range of LVEDV [30]. Consequently, changes in A_c will consistently indicate changes in LVEDV, although an individual estimate of LVEDV derived from A_c may be greater or less than the actual LVEDV. Therefore, we recommend using transoesophageal echocardiography to estimate change in A_c as a direct indicator of change in LVEDV, but not as a method to derive absolute LVEDV.

When subsequent measurements of LVEDV are to be compared, an identical cross section must be viewed, and the relative function of the imaged and non-imaged areas of the heart must be constant. In a normal ventricle, A_c at the mitral level is greater than that at the papillary levels. We measure A_c at the tips of papillary muscles because A_c is near maximum at this point and septal contraction is still present. Above this level, the septum becomes membranous and does not contract.

Despite these limitations, LV preload is better estimated by transoesophageal echocardiography than by measurement of PAOP. In the study of 32 patients undergoing cardiovascular surgery, we found that the estimates of stroke volume (compared with thermodilution estimates) obtained from the short-axis echocardiographic cross section were consistent in 91% of patients, indicating the validity of the measurements [1]. In contrast, end-diastolic A_c correlated with PAOP in only 23% of patients. Because marked changes in LV compliance occur during cardiovascular surgery, PAOP becomes an inadequate guide to LV preload. In a research setting transoesophageal echocardiography provides a practical alternative.

Afterload

In the isolated or intact heart, the velocity and extent of ejection are inversely related to afterload, the force required to eject blood from the LV into the aorta. This force per unit area of myocardium is the systolic wall stress and is determined by the Laplace relationship: wall stress is related directly to the product of systolic arterial pressure and the radius of the LV, and inversely related to LV muscle mass or thickness. The traditional indices of LV afterload, systolic arterial pressure (SAP) and systemic vascular resistance (SVR), are unreliable measures of afterload because they fail to account for the influence of LV radius and wall thickness. For example, the hypertensive patient who has normal LV function usually has normal afterload systolic wall stress or force per unit of myocardium because of compensatory LV hypertrophy. Echocardiography can provide reliable estimates of LV radius and thickness [6, 17, 38] which will yield valid estimates of systolic wall stress. For instance, Reichek and his colleagues [17] found that systolic wall stress estimates calculated using precordial M-mode measurements and arterial pressure determined by cuff correlated closely ($r = 0.97$) with estimates made from angiographic parameters and LV pressures. St John Sutton's group [19] have published a two-dimensional correlate of this formula which can be applied to short-axis echocardiograms to allow calculation of meridional systolic wall stress (SWS_m):

$$SWS_m = (1.3)(SAP)(A_c)/(A_t - A_c)$$

where A_c is the cross-sectional area of the LV cavity and A_t is the total area of LV enclosed by epicardium and the right side of the septum. The denominator of the equation, $(A_t - A_c)$, is the cross-sectional area of the LV myocardium (fig. 3). This equation is valid if the cross section of the LV is approximately round and all segments contract equally.

Afterload, like preload, heart rate and contractility, is a primary determinant of myocardial oxygen consumption. Failure to assess afterload adequately may handicap the accurate interpretation of cardiovascular studies. In a study of 38 patients monitored by transoesophageal echocardiography during carotid endarterectomy, we randomly assigned phenylephrine or "light anaesthesia" to augment arterial pressure [23]. Patients given phenylephrine had significantly higher systolic wall stress values (172 ± 57 (SD) v.

100 ± 44 dyn $\text{cm}^{-2} \times 10^3$) and a higher incidence of myocardial ischaemia. The values in both groups for SAP, heart rate and carotid back ("stump") pressure were similar. Thus the most likely causes of a higher incidence of ischaemia were phenylephrine administration, different depth of anaesthesia or a significant difference in afterload. Had afterload been evaluated by SAP alone, the third, and perhaps most important, of these causes would have been overlooked.

Contractility

Anaesthetics may depress LV contractility directly, or indirectly by decreasing endogenous concentrations of catecholamines. However, assessing contractility is difficult because the readily available indicators are confounded by the changes anaesthetics induce in LV loading conditions. Echocardiography offers a number of approaches to this problem. First, it reliably estimates LV ejection fraction [6, 28, 33] and velocity of LV contraction [15, 16], while simultaneously producing the information necessary to assess preload and afterload, the factors which alter the direct relationship between these indices and contractility. Echocardiography can therefore provide fairly direct information about anaesthetic effects on contractility. In a study of 24 ASA I or II patients undergoing elective surgery, echocardiographic evaluation revealed that increasing concentrations of halothane, enflurane or isoflurane consistently decreased the velocity of LV contraction simultaneously with no change or a decrease (isoflurane) in systolic wall stress and no change in preload or heart rate [2]. Thus all three anaesthetic agents could be seen to depress LV contractility.

Suga and Sagawa [29] have introduced a second approach, an analysis of the pressure-volume ratio of the LV during systole which yields estimates of contractility that are independent of LV loading conditions. Because this ratio is most sensitive to changes in contractility during late systole, end-systolic pressure and volume are usually evaluated. Varying preload or afterload provides multiple points for the plot of pressure v. volume, which results in a linear relationship having a slope believed to be the best available *in vivo* index of LV contractility. Echocardiography is ideal for this application because it provides consistent estimates of LV volume. Moreover, the substitution of SWS_m for LV pressure in the pressure-volume analysis is both

valid and advantageous [18]. First, SWS_m is the force per unit of myocardium, and produces estimates of contractility that are independent of the size of the heart or mass of myocardium. Second, compared with SAP, smaller changes in preload or afterload are required to produce significant changes in SWS_m . The application of the pressure-volume ratio to precordial echocardiographic evaluation of contractility in man has been successful [30]. Studies using this method with transoesophageal echocardiography to evaluate anaesthetic effects are in progress.

It should be noted that the quantitative parameters discussed for contractility, afterload and preload are valid only if their underlying assumptions remain valid. For example, estimates of LV volume are critically dependent on echocardiographic imaging of the appropriate cross section. Estimates of systolic wall stress will be invalid in the presence of abnormal segmental contraction. Normal function of the cardiac valves also may be important. During aortic stenosis, for example, systolic wall stress estimates derived non-invasively will be lower than the actual wall stress values. Similarly, ejection fraction measurement will overestimate contractile function during mitral regurgitation. Our preliminary work with colour-coded Doppler flow imaging suggests that this new modality will provide a sensitive technique for detecting mitral or aortic valve dysfunction. In the meantime, quantitative Doppler techniques are highly reliable, albeit somewhat time consuming, in detecting valvular function [3, 9–11, 26, 35, 39], and we have succeeded in assessing intraoperative mitral regurgitation using transoesophageal Doppler echocardiography [22].

Echocardiography thus provides the means to evaluate LV preload, afterload, contractility and valvular function quantitatively. The methods developed for precordial echocardiography are applicable to transoesophageal techniques. However, precordial echocardiographic data can be obtained before induction of anaesthesia, but most investigators do not initiate transoesophageal echocardiography studies until after induction. The short-axis cross sections obtained with both types of transducer are usually comparable. The fundamental advantage of echocardiography over traditional techniques is the ability to image LV structure and function directly.

EVALUATION OF REGIONAL LV FUNCTION

Segmental wall motion

Tennant and Wiggers [32] first described the association of segmental wall motion abnormalities and myocardial ischaemia in 1935. Ischaemic segments of myocardium exhibit abnormal inward wall motion or thickening during systole [7, 21]. Although focal myocarditis and certain rare infiltrative disorders and myocardial tumours also may produce segmental wall motion abnormalities, ischaemic heart disease is the most common cause. The presence of an akinetic (non-contracting) or dyskinetic (paradoxically moving) LV segment will usually indicate a previous infarction or a scar [36], while the development of new segmental wall motion abnormalities, for example, during a stress test, will almost certainly reflect myocardial ischaemia [14]. Because two-dimensional echocardiography reliably detects segmental wall motion abnormalities, it plays a vital role in the evaluation of patients who have ischaemic heart disease [12–14, 36].

Echocardiographic interpretation of segmental wall motion abnormalities is critically dependent on the reviewer's ability to distinguish between segmental motion of the endocardium resulting from contraction of underlying myocardium, and motion generated by the translational and rotational movement of the heart. The reviewer must be able to evaluate the abnormalities in a moving frame of reference which translates and rotates in perfect synchrony with the heart. Unfortunately, no available automated wall motion analysis system can adequately compensate for these two types of movement in transoesophageal echocardiographic cross sections, and we must continue to rely on qualitative analysis by experienced observers. However, when we compared the outcome of monitoring by echocardiography with monitoring by electrocardiography (ECG), we found the echocardiographic method far superior in detecting myocardial ischaemia. We studied 50 patients at high risk for myocardial ischaemia during coronary artery or major vascular surgery, and 10 low-risk patients [24]. At predetermined intervals, we recorded echocardiograms and multi-lead ECG, both of which were evaluated by "blinded" observers. We diagnosed the onset of myocardial ischaemia if the ST segment changed more than 1 mm in any ECG lead or if segmental LV systolic function worsened by more than 1 class according to the following scale: 1 = normal,

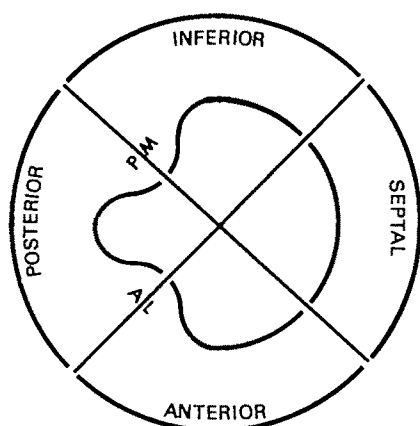


FIG. 4. Schematic cross-sectional view of the left ventricle at the level of the papillary muscles depicting the quadrants into which the ventricle is divided and the corresponding walls. PM = posterior medial papillary muscle; AL = anterior lateral papillary muscle.

2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. Our echocardiographic analysis system was a modification of that of Van Reet [34]. Using a floating reference system guided by the papillary muscles, we divided the cross-sectional image into four segments (fig. 4). A segment was judged to contract normally if its imaginary radius to the centre of the LV shortened by more than 30% and the segment wall thickened considerably. Mild hypokinesis was determined by shortening of the radius by 10–30% and slightly reduced wall thickening, and marked hypokinesis by less than 10% shortening of the radius and minimal wall thickening. Akinesis was defined by no shortening of the radius and no wall thickening, and dyskinesis by outward segment movement and thinning during systole. These analyses were visual estimates of endocardial motion and myocardial thickening. Two observers independently analysed the ECG and echocardiogram without knowledge of either the patient's identity or clinical course. Of the high-risk patients, six had intraoperative ST-segment changes diagnostic of ischaemia, whereas 24 revealed new segmental wall motion abnormalities indicating ischaemia. No high-risk patient experienced an ST-segment change before or in the absence of a corresponding segmental wall motion abnormality. Three of the 50 patients suffered intraoperative myocardial infarction during operation and all three had an abnormality develop and persist in the cor-

responding area of myocardium. Only one of the three had any intraoperative ST-segment change. For 21 of 50 patients, coronary anatomy was known, and segmental wall motion abnormality never developed in areas of the heart served by insignificant lesions. Among the 10 healthy patients, there were no motion abnormalities or ST-segment changes indicative of ischaemia, and no myocardial infarctions. The detection of intraoperative myocardial ischaemia is thus more reliable with two-dimensional transoesophageal echocardiography than with multi-lead ECG.

Segmental myocardial perfusion

Anaesthesia and the stress of surgery may alter the distribution of myocardial blood flow. Echocardiography provides a unique method for tracking the distribution of myocardial blood flow without interrupting clinical care. Newly developed echocardiographic contrast agents make it possible [5]. Sonicated (producing 4- μ m air bubbles) Renograffin-76 was injected to the root of the aorta or left atrium in patients undergoing cardiovascular surgery, and produced a flow of 4- μ m air bubbles [25]. The distribution of the microbubbles embedded in the myocardium was recorded with transoesophageal echocardiography and evaluated quantitatively. The microbubbles consistently produced contrast enhancement of the myocardium and caused no adverse effects. Because the microbubbles collapse within minutes, the study can be repeated. Other preliminary studies in man suggest that this method assesses accurately the distribution of myocardial blood flow [27]. Newer contrast agents are expected and, unlike previous ones, will be structured to survive transit through the pulmonary circulation. With these newer agents, peripheral injection of the contrast should produce echocardiographically detectable "maps" of myocardial perfusion.

CONCLUSIONS

Recent results of intraoperative studies using two-dimensional transoesophageal echocardiography indicate that the technique offers monitoring capabilities that are superior to those of traditional monitors of LV preload, afterload, contractility, valvular function and segmental myocardial contraction. Both clinical care and research efforts are likely to benefit from the application of this new technique. Unlike previous techniques, two-dimensional transoesophageal echocardiography

provides direct images of LV structure and function; using these images, anaesthetists should attain a clearer more precise knowledge of the effects of anaesthetics on LV function.

ACKNOWLEDGEMENT

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DOPPLER FLOW DETERMINATION

A. VIELI

In contrast to the more established methods for blood flow determination, the standard ultrasound procedures are non-invasive. Having become relatively easy to use with the advent of duplex-type combinations of imaging devices and Doppler instruments, they have gained considerable interest over the recent years. As with all quantitative procedures, the basic question refers to the accuracy of the diagnostic information provided.

The present paper concentrates on the measurement of blood volume flow rate by means of conventional (not two-dimensional colour mapped) Doppler ultrasound. After summarizing the fundamental principles of Doppler flow assessment, it deals with the question of accuracy from the points of view both of clinical results and of basic physical problems.

BASIC PRINCIPLES OF DOPPLER ULTRASOUND

Figure 1 shows an example of the on-line information a duplex-system can provide to the user. In an overlay on top of a conventional sector scan echogram, local blood flow velocities are indicated as horizontal deflections of a vertical line. From these local velocity measurements the computer determines a volume flow curve. In principle, integrating this flow curve over the cardiac cycle yields the stroke volume (SV). In this example the numerical value for the stroke volume is suppressed because its absolute accuracy was not considered adequate.

Conventionally, stroke volume is determined by multiplying the cross-sectional area of the aorta by the velocity of the erythrocytes present in this cross-section (fig. 2). The cross-sectional area is measured by conventional echography, while the velocity of the erythrocytes is estimated from the Doppler shift in an ultrasonic echo signal. A pulsed Doppler system relates the

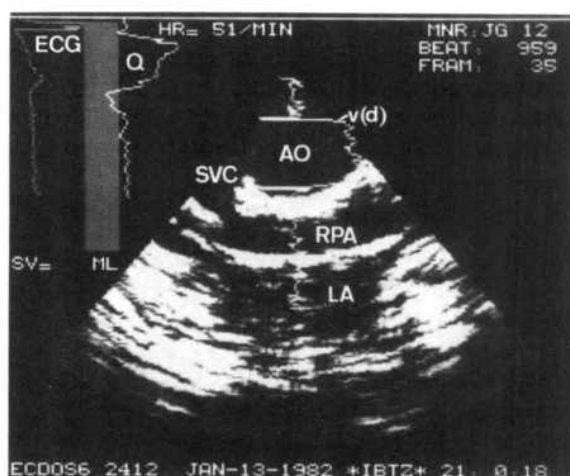


FIG. 1. Duplex Information of a Doppler-echocardiography system. The display combines the structural image (AO = aorta; RPA = right pulmonary artery; SVC = superior vena cava; LA = left atrium) with velocity information as a function of depth along the central fan beam ($v(d)$). The magnitude of the measured velocity is indicated by the horizontal deviation of the $v(d)$ curve from a straight vertical line. In the upper left corner a computed volume flow tracing (Q) is plotted in parallel with the ECG with the time running from top to bottom. (Annotations not mentioned describe measurement conditions irrelevant in this context.)

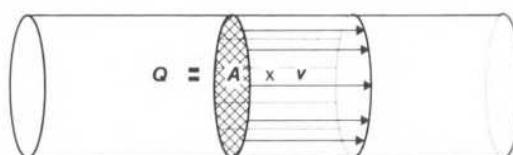


FIG. 2. Basic procedure for the determination of the flow rate. The flow rate Q in a vessel can be obtained by multiplying the cross-sectional area A by the velocity v of the blood contained in this cross-section. The two quantities to be measured are thus A and v .

change in the echo delay between successive bursts to a corresponding change in the distance between the transducer and a reflector. Thus, only axial displacements of the reflector give rise to a Doppler signal, while radial components of the velocity go undetected. This effect is usually

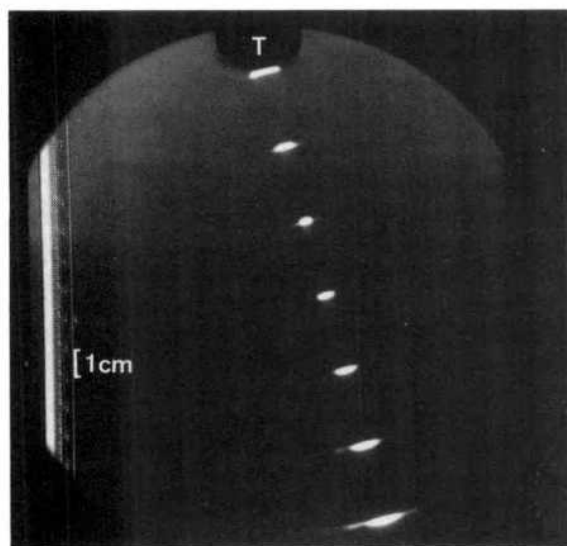


FIG. 3. Ultrasonic pulse dimensions. This Schlieren-photograph visualizes an ultrasound pulse at different distances from the transducer (T). The size of the bright spots imaging the transmitted pulse can be considered typical for a modern phased array scanner. As indicated by the scale on the left, the lateral width of a pulse is of the order of 1 cm, whereas the axial length is of the order of 2 mm. The variation of the lateral dimensions with depth corresponds to focusing at about 7 cm from the transducer.

compensated for by dividing the measured velocity by the cosine of the angle of incidence. As a consequence it is necessary to measure not only the Doppler shift, but also the angle between the ultrasound beam and the local velocity vector.

Spatial resolution of an ultrasound system has an essential impact on the accuracy of both the echographic measurement of the cross-sectional area and the velocity determination. As indicated in figure 3, typical ultrasound pulses exhibit lateral widths of the order of 1 cm and axial dimensions of a few millimetres. The shapes of the pulses may vary with space, the instrument utilized and the mode in which it operates. It should be noticed, however, that the lower limit of the beam width in today's equipment is of the order of several millimetres and, as such does not permit a very high resolution. On the other hand, the upper limit of resolution is considerably less than the diameter of the adult aorta, so that the cross-sectional average velocity is usually estimated on the basis of restricted samples only.

Three different data acquisition modalities are available for Doppler measurements. Figure 1

shows the display of a multigate system. This type of equipment probes the local velocities at multiple locations along the ultrasound beam to provide a spatial velocity profile. By contrast, a single channel device measures the velocity at one given depth range only, but the length of its sample volume can usually be adjusted by the operator. The output of this modality is commonly given by a velocity spectrum as a function of time plus additional curves indicating the instantaneous mean or maximum velocity, or both. Both pulsed varieties are limited in high velocity applications. If the reflector moves faster than a certain limit, the relative delay increment of successive pulse echos is so large that it can no longer be determined unambiguously. This effect is called aliasing. The third modality is continuous wave Doppler which requires twin transducers, one to transmit permanently and the other to receive permanently. At the cost of losing range resolution, continuous wave instruments overcome the aliasing problems associated with pulsed systems.

REVIEW OF CLINICAL RESULTS

A review of the literature [2] has shown that there are a number of studies comparing ultrasound data with quantitative measurements of cardiac output. The results reported are generally good or excellent for measurements in the aorta, only slightly worse for those in the mitral valve area and somewhat worse for those in the pulmonary artery. For the present paper, data from 20 studies [5–24] (special reference list) were considered, which comply with the following requirements: they compare various types of Doppler measurements with invasive results; they report absolute results for flow; and the measurements are made in the aorta. The correlations of Doppler *v.* invasive methods such as Fick, indicator dilution, electromagnetic flowmetry or volumetric measurements by beaker and stopwatch are summarized in figure 4. The results are grouped according to the subjects evaluated. Correlation worsens from phantoms to animal models to children and finally to adult patients. Moreover, as most of the studies excluded patients with disorders of the left ventricular outflow tract or the aortic valves, it must be anticipated that the correlation for unselected patients would be even worse.

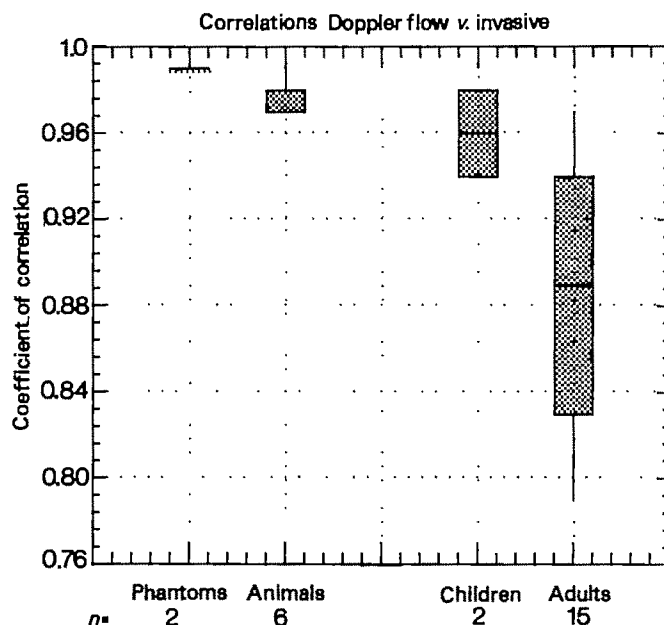


FIG. 4. Overview of clinical results. Correlations of volume flow measurements in the aorta between Doppler procedures and different invasive techniques based on papers of 20 authors [5-24]. The distributions of the coefficients of correlation are presented as boxes extending upwards and downwards from the median line to include 50 % of the samples of each group. The vertical lines cover the remaining range of reported values. The groups as well as their number of correlation coefficients are given at the bottom of the figure.

When interpreting these comparisons, one should keep in mind that the established invasive "gold standards" may not always be so golden [3].

The above results provide only part of the information necessary to investigate the accuracy of Doppler methods. In order to be able to assess the value of the measurement in a given patient, it is important to understand the basic mechanisms which lead to erroneous results.

FUNDAMENTAL SOURCES OF ERROR

As mentioned earlier, three quantities must be measured for the calculation of flow rate, namely the angle of incidence, the cross-sectional area of the vessel, and the mean transluminal blood flow velocity. Each of these is associated with a potential error.

In a clinical situation the angle of incidence relative to a three-dimensional vascular structure is not easily estimated from a two-dimensional echogram. According to the shape of the cosine function, the error with regard to the flow

measurement varies only from 0 to -6 % when the angle between the ultrasound beam and the velocity vector is in the range -20° to $+20^\circ$, but at a nominal angle of incidence of 45° a deviation of $\pm 20^\circ$ leads to flow errors between -40 % and +28 %. An additional angular problem can result from non-laminar flow conditions which are likely to occur behind an obstruction. In these cases the local velocity vector is not necessarily parallel to the vessel wall and can therefore not be fully assessed with the aid of the echogram.

A fundamental problem in the determination of the cross-sectional area is the fact that this area is commonly computed from the echographically measured vessel radius. By squaring the radius one squares the error as well. Such an inaccuracy can occur as a consequence of the limited spatial resolution of the ultrasound equipment. Under realistic assumption, the area error may be of the order of ± 10 to 20 % (fig. 5). As the vessel walls are somewhat elastic, the cyclic variations of the vascular diameter resulting from pressure changes should also be taken into account. Furthermore, in veins or obstructed arteries the luminal shape

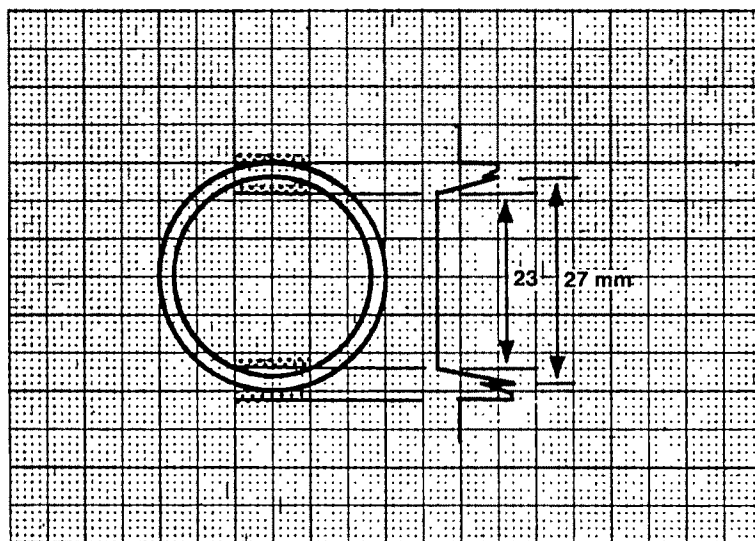


FIG. 5. Errors in the diameter measurement attributable to finite pulse dimensions. Because of the finite pulse dimensions, a gradual transition occurs when the ultrasound pulse (shaded with dots) enters or leaves the vessel walls. The essential features of the variation of the echo as a function of depth are depicted on the right. Depending on the machine settings, the apparent internal diameter can vary from 23 to 27 mm in this simplified example. This 15% variation yields a 33% uncertainty for the cross-sectional area.

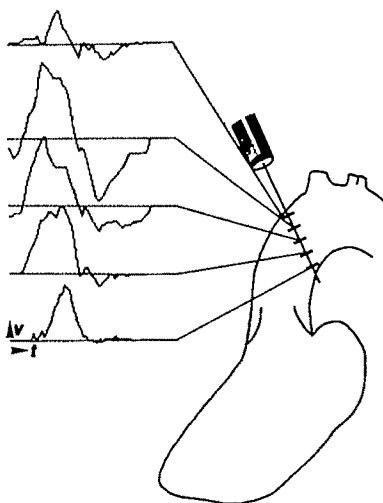


FIG. 6. Site dependence of velocity tracings. This example recorded in a patient with severe aortic insufficiency shows the velocity, v , as a function of time t as recorded simultaneously at five different locations across the aortic lumen.

may deviate considerably from the circle commonly assumed for the area calculation.

Figure 6 illustrates the irregular transvascular velocity distribution observed in a patient with severe aortic insufficiency. Depending on the site

at which the velocity is sampled, one can record either considerable retrograde flow or a fairly normal pattern. In such patients with highly irregular velocity distributions, the measurements become strongly dependent on the size and the

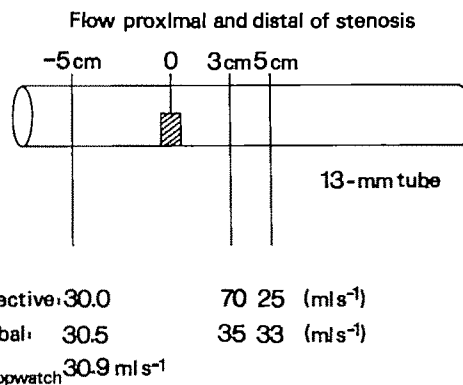


FIG. 7. Effect of an artificial obstruction. For this experiment an obstruction was created within a rigid tube in a fluid mechanical bench model. The volume flow rate of bovine blood pumped through the tube was determined by beaker and stopwatch as well as by Doppler ultrasound. Two different Doppler modalities were applied at three different sites. The global modality had a wide pulse covering the entire lumen of the tube and the conventional multigate procedure (selective) involved a narrow beam. The resulting volume flow rates are given in the figure.

position of the sample volume. A phantom experiment documented in figure 7 shows that errors of the order of 100 % can occur in extreme cases if the velocities are merely sampled along a relatively narrow beam as usual. By contrast, an experimental wide beam covering the entire vessel keeps the error within 20 % bounds under the same haemodynamic conditions.

From the above considerations errors up to 100 % cannot be excluded in an individual measurement with the equipment of today, especially if the person utilizing the method is not aware of adverse measurement conditions.

DISCUSSION AND CONCLUSIONS

The considerable discrepancy between the serious worst case errors anticipated from basic measurement problems and the good correlations reported clinically require some further elucidation. First, one should keep in mind that some cardiac patients exhibit almost normal velocity distributions [4]. In these patients, usually without major disorders in the region of the measurement site, the errors are far below the worst-case numbers. Second, coefficients of correlation are average values. They do not give a clear indication as to the worst measurement, which can be estimated from the plots given in some references as being associated with a discrepancy in excess of 50 %. Moreover, in some of the studies the cardiac output range covered extends beyond the usual limits as a result of medication. This usually improves the r value, but may not be representative for a general patient population [1].

Thus the following conclusions can be drawn: (1) with the equipment available today, reliable cardiac flow measurements having an absolute accuracy of 10–20 % can be obtained only in specific groups of patients; (2) the Doppler procedure must be carefully selected to take account of the haemodynamic condition of the patient; (3) the quality of the results can be improved by orienting the beam directions parallel to the flow and by directly assessing the cross-sectional area instead of the vascular diameter. Equipment optimized to quantify the instantaneous mean velocity of the entire vascular cross-section is being developed to alleviate the problem of probing irregular flow distributions. Nevertheless, whenever feasible, multiple independent measurements should be averaged to reduce the uncertainty of the result.

SUMMARY

Doppler ultrasound provides a non-invasive alternative to the established methods of blood flow measurement. The standard principle of the Doppler–echographic determination of volume flow rate is based upon the assessment of three quantities: the vascular cross-section, the angle of incidence of the ultrasound relative to the direction of the velocity vector, and the cross-sectional average velocity. In the literature reporting comparisons between Doppler and invasive cardiac output measurements, correlation coefficients ranging from 0.8 to 0.95 are given for adult patients. Error limits of less than 20 % for individual measurements, however, require a skilful investigator, a high quality instrument, and an appropriate subject. From a technical point of view, the highest accuracy is achieved by directing the ultrasound beam parallel to the flow, by measuring the true cross-sectional area instead of the diameter, and in the presence of well-behaved transluminal blood velocity distributions.

ACKNOWLEDGEMENT

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MEASUREMENT OF VENTRICULAR EJECTION FRACTION IN THE ACUTELY ILL

J. L. VINCENT

The ejection fraction is an index of ventricular function relating stroke volume to end-diastolic volume. Ejection fraction is influenced not only by myocardial contractility but also by loading conditions [7].

Ejection phase indices are relatively insensitive to changes in preload, but are more affected by changes in afterload. The end-systolic volume is altered by the developed force so that the extent of shortening decreases if the afterload increases, even if contractility is not altered. Changes in heart rate can also influence ejection fraction [6]. In the early stages of cardiac failure, cardiac function can be maintained by compensatory mechanisms including ventricular dilatation and hypertrophy, so that ejection fraction might not be altered. Measurements of ejection fraction also assume that the ventricle is homogenous and does not show regional abnormalities associated, for instance, with ischaemia. Hypokinetic or even akinetic areas can be masked by increased function in other areas.

APPLICATIONS

Left ventricular ejection fraction is widely used to assess and quantify left ventricular performance in patients with congestive heart failure, coronary heart disease or other cardiac abnormalities. Left ventricular ejection fraction also has a prognostic value, especially in patients with coronary heart disease. Similarly, *right ventricular* ejection fraction can be used to assess right ventricular performance in the absence of pulmonary hypertension. In patients with chronic pulmonary disease, measurement of radionuclide right ventricular ejection fraction has also been suggested

as a means of diagnosing pulmonary hypertension non-invasively [1].

METHODS OF MEASUREMENT

Contrast angiography

Left ventricular ejection fraction is usually calculated from angiographic measurements of left ventricular volumes. The normal left ventricular ejection fraction is 65–70%. In other words, stroke volume equals two-thirds of the end-diastolic volume, which is normally around 125 ml [7].

Measurement of ventricular volumes is facilitated by the regular shape of the left ventricle. Rapid injection of contrast material to the heart can transiently influence ventricular performance. However, this effect can be minimized, especially by using digital subtraction radiography.

Right ventricular ejection fraction is more difficult to measure because of the complex right ventricular shape. Single plane angiograms are not very accurate, but reliable measurements can be obtained from biplane angiograms. Nevertheless, right ventricular angiograms are seldom indicated in adults, and other methods are preferred.

Nuclear angiography

The underlying principle of the radionuclide methods for determination of ventricular ejection fraction is that the radioactivity in the ventricular area is proportional to the ventricular volume, so that changes in radioactivity are proportional to ejection fraction. The major advantage of the radionuclide measurements is their relative independence of ventricular geometry. The most commonly used radionuclide is technetium 99m, which has a half-life of 6 h. Ventricular ejection fraction can be measured either after synchronization of the acquisition of images with the cardiac cycle (by multigated equilibrium blood

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pool studies) or during rapid recording of the first passage of the radionuclide tracers. The first-pass techniques usually yield a slightly lower value [3]. The major technical limitation of the radionuclide techniques is the difficulty of determining with precision the onset and the end of systole and diastole. The method is also submitted to variability both within and, especially, between observers, generally estimated to be between 5 and 10%.

Nevertheless, radionuclide angiography represents a useful non-invasive alternative to contrast angiography to assess *left ventricular* ejection fraction. It has even become the method of choice for measurement of *right ventricular* ejection fraction, since it minimizes the problem of complex geometry and shape of the right ventricle. Again, the technique involves changes in radioactivity within the right ventricle rather than direct volume measurements. However, it is necessary to make simultaneous measurements of cardiac output and stroke volume by the thermodilution technique in order to calculate right ventricular end-diastolic volume.

The first-pass technique is limited by the restricted counting time, but avoids the superimposition of the right atrial blood pool, so that it is usually the preferred method of determining right ventricular ejection fraction.

Echocardiographic techniques

Echocardiographic measurements of ventricular volumes assume there is a predictable relationship between ventricular diameter and volume, so that their accuracy is limited in the presence of regional abnormalities. Determination of *right ventricular* volumes by echocardiography has been found reliable [9], but the image acquisition is often unsatisfactory in acute conditions.

Thermodilution studies

As mentioned previously, a measurement of ejection fraction is not very meaningful in the absence of simultaneous measurement of intravascular pressure and flow. Alterations in ejection fraction are difficult to interpret without estimation of preload which influences end-diastolic volume, and afterload which influences stroke volume and end-systolic volume. This is especially so for the right ventricle, which is very sensitive to increases in its afterload. Many studies have, therefore, combined determinations of *right*

ventricular ejection fraction by radionuclide techniques with measurements of intravascular pressures and cardiac output obtained by invasive haemodynamic monitoring using pulmonary artery catheters. These combined measurements allow one to calculate end-diastolic volumes by dividing the stroke volume measured with the thermodilution technique by the radionuclide ejection fraction.

Recent technical developments have enabled the routine measurement of *right ventricular* ejection fraction to be made by the thermodilution technique [4, 8]. The method involves the use of modified pulmonary artery catheters equipped with fast response thermistors which accurately reflect beat-by-beat changes in blood temperature within the pulmonary artery. From the thermodilution curve, right ventricular ejection fraction can be easily calculated either by measuring the successive temperature plateaux or by using a simplified algorithm based on exponential curve analysis [8].

The technique depends on adequate mixing of the cold water bolus in the cardiac chambers. Errors from this source have been reduced by using a catheter with three exit ports, so as to improve the dispersion of the cold water bolus injected above the tricuspid valve [8].

In critically ill patients requiring haemodynamic monitoring, this technique has the advantages of simplicity and of allowing repetitive measurements during the course of the acute illness. It also provides simultaneous measurements of pulmonary artery pressures, right atrial pressure and, especially, stroke volume, so that right ventricular end-diastolic volume can be calculated. Right ventricular ejection fraction measurements obtained by the thermodilution technique correlate well with those obtained by radionuclide techniques [4, 8]. This technique has been found useful for the clinical study of changes in right ventricular function, or in right ventricular pressure-volume relationship induced by various agents [2, 5]. Measurement of right ventricular volumes can guide both fluid infusion and the administration of vasoactive agents in the operating room or in the intensive care unit. It has potential value in various specific conditions, such as after cardiac surgery, during titration of PEEP in acute respiratory failure or in right ventricular myocardial infarction. It is, therefore, considered to be a useful adjunct to haemodynamic monitoring.

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SPECIES DIFFERENCES

T. H. STANLEY

Assessment of the effects of anaesthetics on myocardial function is difficult using *in vivo* animal models because different animals can have enormously different anaesthetic requirements [5-8, 15]. Furthermore, many, if not all, of the analgesics, tranquillizers and anaesthetics available and commonly used to sedate, immobilize or anaesthetize different species often produce widely different cardiovascular responses [5]. The reasons for these often dramatically different requirements and cardiovascular effects are not entirely clear, but may be related to differences in basal temperatures, basal metabolic rate or both, the psychological impact of confinement and captivity, differences in what wildlife biologists call "wildness" or excitement, the state of hydration, heightened or depressed abilities to perceive pain, the use of trained or untrained animals, the effects of training on stress, excitement and CNS activity in different species, tolerance, age, the weight of the animal, and the relative distribution of cardiac output to highly vascularized tissues such as the brain and spinal cord as well as to other large tissue masses, such as muscle [1-8, 11, 15].

Some investigators have determined that dose scaling may be best determined by the minimal energy cost or basal metabolic rate of animals [11]. Data are now available which indicate that passerine birds have more than 50% greater energy requirements than non-passerine birds. These studies indicate that non-passerine birds have a minimal energy requirement that averages almost 10% greater than placental animals, that marsupials have even less of a minimal energy requirement, and reptiles have the lowest metabolic rates [11]. These differences are only partially related to differences in body temperature.

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Training, familiarity with humans, lack of stress, or captivity can also have an impressive effect on the doses of drug needed for tranquillity, immobilization or anaesthesia. Indeed, a recent experiment in 24 newborn elk calves, clearly demonstrated the effects that "wildness" (excitement) may have on anaesthetic (immobilizing) requirements (Stanley TH, unpublished data). The animals were divided into two groups, one of which were hand-reared and the other placed with their natural mothers and allowed to grow to yearlings (1 year of age). At approximately 13 months of age, all the animals were collected and evaluated in an out-door field laboratory. The hand-reared animals required only one-third of the dose of xylazine than did the wild animals for immobilization. The hand-reared animals also became immobilized twice as fast (table I).

Most veterinarians and wildlife biologists are also aware of the important psychological impact of confinement. A case from Kruger National Park clearly demonstrated this impact on doses of major tranquillizers required for immobilization [6]. There are many examples of this, but the case in Kruger National Park emphasized the point. The investigators immobilized a bull rhinoceros which had been in captivity for several weeks with benzodioxane 1.25 g and acetylpromazine 100 mg i.m. Immobilization was complete in 10 min. However, the same dose administered i.m. to a cow rhinoceros, which was less than two-thirds the size of the bull, in the field did not stop her from running even after 1 h. Confinement clearly decreases the dose of any immobilizing agent

TABLE I. Elk immobilization with xylazine i.m. (Means $\pm$ SD)

	Hand-reared	Wild
Immobilization time (min)	9.3 $\pm$ 3	18 $\pm$ 5
Immobilization dose (μ g kg ⁻¹)	0.37 $\pm$ 0.05	1.32 $\pm$ 0.2

TABLE II. Doses of carfentanil required for immobilization in a number of genera

Genus	(Family)	Weight (kg)	Dose ($\mu\text{g kg}^{-1}$)
	(Rhinos)	1600	0.7
	(Bovinae)	680	7.7
Eland	(Tragelophinae)	180	13.0
Gnu	(Alcelaphinae)	140	10.2
Waterbuck	(Reduncinae)	116	18.0
Oryx	(Hippotraginae)	111	23.2
Deer	(Cervidae)	63	13.6
Sheep/goats	(Caprinae)	57	21.3
Gazelle	(Antelopinae)	37	29
Ostrich	(Avian)	125	24

TABLE III. Doses of carfentanil required for immobilization in the sub-family Antelopinae

Species	Weight (kg)	Dose ($\mu\text{g kg}^{-1}$)
Impala	56	17
Addra	52	15
Mhorr gazelle	49	25
Roosevelt gazelle	47	27
Soemmering's gazelle	45	26
Springbok	(27)	(37)
Thomson's gazelle	25	30
Persian gazelle	22	33
Slenderhorne gazelle	21	43
Sand gazelle	18	33

necessary for immobilization [7, 15]. However, the mechanism producing these changes is unknown. It is speculated that confinement decreases an animal's perception of its ability to escape. Furthermore, the smaller the confining area the smaller the concentration of drug necessary for immobilization [15].

In general, doses of immobilizing agents and anaesthetics decrease (on a weight basis) as the size of the animals increases. This can be seen in animals of different genera (table II) or different species within a single sub-family (table III).

Some species experience remarkably different ventilatory and cardiovascular responses during immobilization than others. For example, dogs are extremely insensitive to the respiratory effects of narcotic compounds and do not become apnoeic irrespective of the dose of fentanyl, etorphine or morphine administered i.v. as a sole analgesic, anaesthetic or immobilizing agent [2, 4, 5, 10, 14]. Indeed, dogs will experience a convulsive episode before sustaining ventilatory depression after high doses of virtually any narcotic. Other species (felines and equines) are excited by opioids, but generally the rate of ventilation is slightly depressed even during the period of excitement [6]. Given the variability in response between different species and the importance of minimizing excitement in attempting to immobilize, tranquilize or anaesthetize untrained animals, it is easy to understand why most veterinarians use mixtures of compounds to immobilize or anaesthetize. Generally, tranquillizers are more effective after capture when excitement is less intense, but, since tranquillizers are very effective in antagonizing excitement, they are often used alone to facilitate handling animals or in combination with an immobilizing agent to enhance speed of immobil-

ization [6, 15]. Tranquillizers are rarely given alone and are rarely effective in the capture of wild animals unless given in enormous doses which can have severe cardiovascular consequences. As a result of the frequent practice of using tranquillizers and immobilizers together (a form of balanced anaesthesia), there are few data available regarding the cardiovascular effects of the different anaesthetics, tranquillizing or immobilizing agents when used alone. However, what data are available suggest that variability seems to be greater with i.m. or i.v. anaesthetics than with the potent inhalation anaesthetics.

In general, potent inhalation drugs produce cardiovascular depression over a reasonably limited range [9, 12]. In addition, responses are similar in most species. Most of the potent inhalation agents have MAC values that are not appreciably different from those in man. In contrast, Weiskopf and colleagues [13] have shown that the MAC of nitrous oxide in swine is more than 2.5 times that of man. The potent inhalation agents generally produce depression of cardiac output, stroke volume, and mean arterial pressure in a dose-dependent fashion in most species [9, 12].

Anaesthetics administered i.v. and i.m. often cause impressively different responses in different species. While most species experience profound decreases in heart rate and small decreases in arterial pressure after large doses of μ receptor stimulating opioids, in the horse these compounds increase arterial pressure and heart rate [6, 15]. This can be minimized by the simultaneous administration of a tranquillizer such as acetylpromazine, but this combination results in significant cardiovascular depression and can lead to severe respiratory and cardiovascular embarrass-

TABLE IV. *Anaesthetizing doses of ketamine*

Species	I.v. dose (mg kg ⁻¹)	Species	I.m. dose (mg kg ⁻¹)
Dog	5-44	Monkey	5-25
Cat	5-44	Mouse	44
Swine	15-20	Rabbit	10-60
Ferret	10-40	Rat	20-40
		Sheep	22

TABLE V. *Anaesthetizing doses of barbiturates*

Species	Drug	I.v. dose (mg kg ⁻¹)
Dog	Pentobarbitone	39-35
	Thiopentone	15-20
Cat	Pentobarbitone	20-30
	Thiopentone	15-20
Swine	Pentobarbitone	20-30
Ferret	Pentobarbitone	35
Mouse	Pentobarbitone	35-70
	Thiamylal	25-50
Monkey	Pentobarbitone	30-35
Rabbit	Pentobarbitone	20-45
Rat	Pentobarbitone	30-40
Sheep	Pentobarbitone	25-30
	Thiopentone	20-25

TABLE VI. *Anaesthetizing doses of chloralose*

Species	Dose
Dog	50-100 mg kg ⁻¹ i.v.
Swine	55-86 mg kg ⁻¹ i.v.
Cat	60-100 mg kg ⁻¹ i.v.
Rat	55 mg kg ⁻¹ i.p.

ment [5-8, 15]. Variability of opioid effect is clearly characteristic of narcotic anaesthesia in man [4]. It may be more evident in other species, for example, the dog. In a recent experiment, Bailey and colleagues have demonstrated that fentanyl is an unreliable anaesthetic in canines except when administered in doses of 3000 µg kg⁻¹ or greater [2]. Plasma concentration necessary for non-responsiveness to tail clamp after i.v. injection in the dog could be as low as 25 ng. In contrast, some animals with plasma concentrations as great as 465 ng ml⁻¹ moved with tail-clamp stimulation. Tables IV-VI give a range of doses for numerous i.v. anaesthetics in a variety of species.

CONCLUSION

Anaesthetic requirements and cardiovascular responses of commonly used tranquillizers, immobilizers and anaesthetics are variable in common laboratory animals as well as domestic and other wild animals. The reasons for this include size, training, hydration, metabolic rate, excitement or wildness, absence or presence of confinement and perhaps many other unknown factors.

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EFFECTS OF BASAL ANAESTHESIA ON CARDIAC FUNCTION

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Schmidt's work in 1938 was considered to be the first to recognize that anaesthesia may influence physiological and pharmacological responses [7]. Despite this early warning, Olmsted and Page [17] reported that, between 1962 and 1964, 90-94 % of cardiovascular studies were still using anaesthetized animals. Although the proportion of investigations performed today in anaesthetized animals is not established, anaesthetized, acutely-instrumented animals are the model most often used. Frequently, concepts are proposed on the basis of data collected in these experimental conditions. Yet the limitations of such an approach are rarely considered. On the contrary, it may be claimed that basal anaesthesia does not interfere with cardiovascular function. Although there were earlier attempts to understand the consequences of general anaesthesia for cardiovascular function, for technical reasons most of the knowledge in this field has been collected only in the past 3 decades. For example, the instruments permitting the development of chronically-implanted animal models for the study of cardiovascular function were developed in the late 1960s. As is often the case, a limited number of groups contributed most to current knowledge.

The effects of anaesthesia on cardiac function have been discussed in a number of reviews. Although humans were the main focus [2, 11, 18], in a few cases other species have also been considered [19]. However, little consideration has been given to the potential effects of basal anaesthesia on cardiac function in animals. Vatner and Braunwald [23] provided an important review of the mechanisms by which general anaesthesia affects cardiovascular function. The consequences of basal anaesthesia have to be evaluated in terms of additive, synergistic and antagonistic effects.

What makes this problem even more complex is that, in most cases, it is not possible to predict the nature of the interaction on the basis of data already available. Briefly, basal anaesthesia may affect cardiac function by its direct effects on the cardiovascular system and by its effects on the remote and local control of circulation. In addition, basal anaesthesia may significantly alter the disposition of endogenously, as well as exogenously, administered substances and drug effects which may also interfere with the responses recorded.

DIRECT EFFECTS OF BASAL ANAESTHESIA ON CARDIAC FUNCTION

In vivo, cardiac function is dependent not only upon the direct cardiac effects of anaesthetics, but also on the anaesthetic-mediated changes in pre- or afterload. Consequently, the direct cardiac effects of anaesthetics may be balanced by simultaneous effects on the remote and local control of circulation.

Anaesthetics such as diazepam, chloralose, pentobarbitone, thiopentone, thiamylal, ether, halothane and methoxyflurane are potent direct negative inotropic drugs; this also applies to ketamine which, *in vivo*, increases cardiac output as a result of a reflex cardiac stimulation. This concept is based mainly on experiments performed *in vitro* using papillary muscle [9] and isolated heart preparations, and *in vivo* using heart-lung preparations [20]. Without questioning the value of these experiments, it must be recognized that—except when decapitation is used as in rabbits, guineapigs and rats—hearts are obtained from anaesthetized animals. When isolated heart-lung preparations are used, the role of basal anaesthesia may be even more important since, in order to set up the preparations, the animals have to be anaesthetized. Thus even in these experimental conditions, the data recorded

may be at least partly dependent on the anaesthetic used before the experiment.

Although it appears that general anaesthetics have less direct effects on vascular smooth muscle, barbiturates and inhalation anaesthetics—especially isoflurane—have been demonstrated to possess direct vasodilator properties. As with most vasodilators, their potency varies with the specific vascular beds [3].

EFFECTS OF BASAL ANAESTHESIA ON THE CENTRAL AND AUTONOMIC NERVOUS SYSTEMS

Although general anaesthetics obviously have profound effects on the central nervous system, it is difficult to assess their role in the overall cardiovascular consequences of basal anaesthesia. For barbiturates it is established that a relationship exists between the concentration of drugs in the plasma and the brain. However, the relationship between the anaesthetic concentration threshold and the concentration which affects the cardiovascular centre remains unknown. Thus it is not possible to determine the nature of the interrelation between general anaesthesia and centrally-mediated cardiovascular function. Recovery from general anaesthesia is unrelated to its duration. In this regard the study performed by Sawyer, Lumb and Stone [22] provides important data. They demonstrated that, following recovery from anaesthesia, cardiovascular and neurological functions are altered for several hours after halothane and methoxyflurane exposure and pentobarbitone injection. Similar effects can be seen with the short-acting barbiturates thiopentone and thiamylal. The mechanisms of these interactions probably include drug accumulation in the heart, vessels and peripheral and central nervous systems. Goldstein and Aronow [10] reported parallel changes in pentobarbitone and thiopentone concentrations in plasma and brain. Although it is possible to define an anaesthetic threshold in terms of a plasma concentration, the relationship between the centrally-mediated cardiovascular changes and the anaesthetic threshold is unknown. One of the few studies to document the effects of anaesthetics on centrally-mediated cardiovascular changes in chronically instrumented dogs was reported by Ngai and Bolme [15]. They demonstrated that barbiturates and halothane depressed responses obtained after stimulation of hypothalamic and mesencephalic vasoactive areas.

Anaesthetics also affect the function of the autonomic nervous system, both centrally and peripherally. Depression of ganglionic transmission appears to be an important mechanism by which anaesthetics alter the function of the autonomic nervous system. Such a depression has been reported with oxybarbiturates [8, 13] and inhalation anaesthetics [21]. Conversely, it seems that thiopentone [8, 13] and urethane [14] have little or no effect on ganglionic transmission. In this respect it is interesting to note that tubocurarine may also affect ganglionic transmission, even at doses lower than its therapeutic threshold [16]. However, the magnitude of the block depends upon the species—it is minimal in dogs [1, 12], while more marked in cats. In addition, tubocurarine appears to have more pronounced effects on the parasympathetic than on the sympathetic system [18].

Another important mechanism by which anaesthetics alter cardiovascular function is their effect on reflex pathways. The baroreflex pathway has been extensively investigated, especially after Vercauteren and Heymans [25] noted that baroreflex function was depressed in the presence of barbiturate anaesthesia. These results were later confirmed by Brown and Hilton [4]. Vatner, Franklin and Braunwald [24] demonstrated that pentobarbitone alters responses from carotid sinus nerve stimulation; in the conscious state the bradycardia induced by stimulation of the carotid sinus nerve is mediated by the parasympathetic system, whereas it is dependent upon a sympathetic withdrawal after administration of pentobarbitone. In addition, recovery from the stimulation is prolonged during pentobarbitone anaesthesia. Other characteristic examples are the effects of such anaesthetics as chloralose and pentobarbitone on chemoreflex-mediated haemodynamic changes [27]. In the awake state, stimulation of the chemoreceptors leads to increases in arterial pressure and iliac vasoconstriction. Although haemodynamic values are similar during pentobarbitone and chloralose anaesthesia, haemodynamic responses to chemoreceptor stimulation are abolished. These findings are of especial interest when considering that anaesthetics alter differently the respiratory response to chemoreflex pathway stimulation. Chloralose and pentobarbitone decrease the centrally-mediated responses, whereas they potentiate the peripheral responses [7].

CONSEQUENCES OF BASAL ANAESTHESIA FOR THE EXPERIMENTAL DESIGN

As stated earlier, the problem of basal anaesthesia is not its relation to the properties of drugs *per se*; its problems are the consequences of carrying out investigations in the presence of anaesthetics and mechanical ventilation and in surgically-stressed, possibly open-chest animals. In these conditions it is not possible to disassociate the role of each factor. The situation is made even more complex by the existence of species specificities in the cardiovascular consequences of basal anaesthesia. Furthermore, the use of anaesthetics differs, depending upon the species. Barbiturates—including pentobarbitone, thiopentone and thiamylal—are often used in dogs, cats and rats for cardiovascular physiology and pharmacology experiments, whereas chloralose is often used in the same species for neurological experiments, discrimination between these two indications being based on the theoretical absence of interference with the corresponding system used. We know that both types of anaesthetic interfere with the cardiovascular and nervous systems. However, the consequences of basal anaesthesia must also be evaluated in relationship with the rationale behind the experimental design. If the procedure is designed toward the assessment of drug effects on cardiac function or on the interactions between vasoactive drugs and anaesthetics, then basal anaesthesia is not suitable. If the goal is to mimic clinical situations, or to assess the drug effects during anaesthesia, then the use of basal anaesthesia may be justified. Even more important seems to be the method by which steady-state conditions can be verified. The use of basal anaesthesia for which a steady state is demonstrated (temperature, fluid balance, haemodynamic and respiratory functions, etc.) is preferable to uncontrolled conditions in awake animals.

EFFECTS OF BASAL ANAESTHESIA ON DRUG DISPOSITION

Although it is established that changes in drug distribution and elimination may affect cardiovascular pharmacology, the effect of basal anaesthesia on drug disposition is not especially considered in its consequences on cardiovascular function. Anaesthetics, surgical stress, carbon dioxide [19] and acid-base balance status are factors which may alter drug disposition. Pento-

barbitone alters catecholamine metabolism. Inhalation anaesthetics affect hepatic clearance of antipyrine, verapamil [5], nifedipine, plasma protein binding of lignocaine, propranolol, diazepam [6], and oxidative biotransformation of aminopyrine [26], fentanyl and propranolol. Chloralose displaces warfarin from its protein binding site. In most cases, the consequences of basal anaesthesia on drug disposition are difficult to predict and are consequently ignored.

CONCLUSION

Basal anaesthesia includes not only the use of premedication and general anaesthetics, but also the physiological and pharmacological disturbances (acute instrumentation, mechanical ventilation, alteration of acid-base balance, etc.) related to the preparation of the experimental model. Except for a limited number of designs in well-controlled conditions, the physiological as well as the pharmacological consequences of basal anaesthesia on cardiac function are unpredictable. Basal anaesthesia not only directly interferes with cardiac function, but also affects the cardiovascular system by effects on vessels and on the central and peripheral nervous systems. Furthermore, basal anaesthesia may have important effects on drug distribution. Hence, investigations conducted in anaesthetized animals are of limited value, since it is not known what interactions will be introduced to the system. In this respect, each experimental design represents a condition which must be studied in itself.

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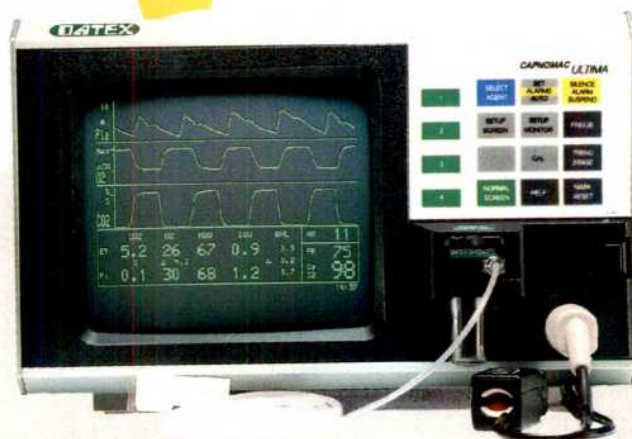
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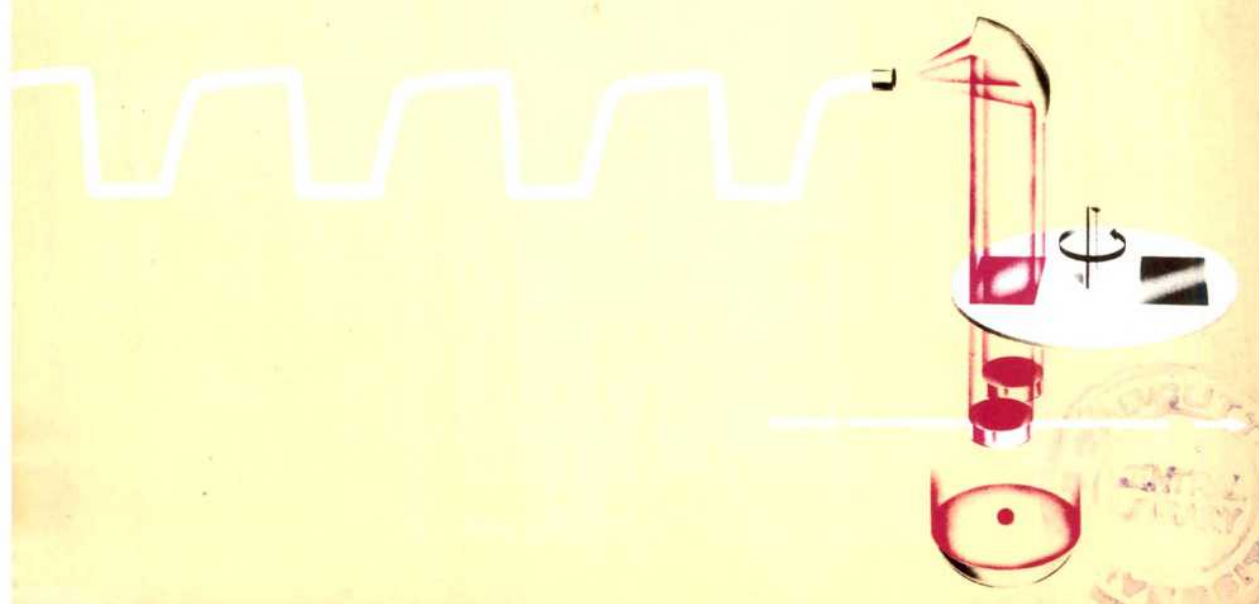
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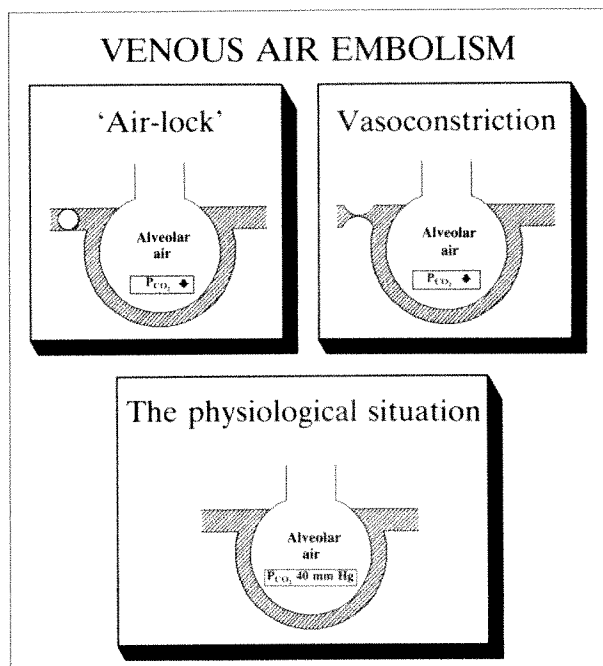


Fig 73

Two pathophysiological mechanisms are involved in the perfusion of the lungs following an air embolism:

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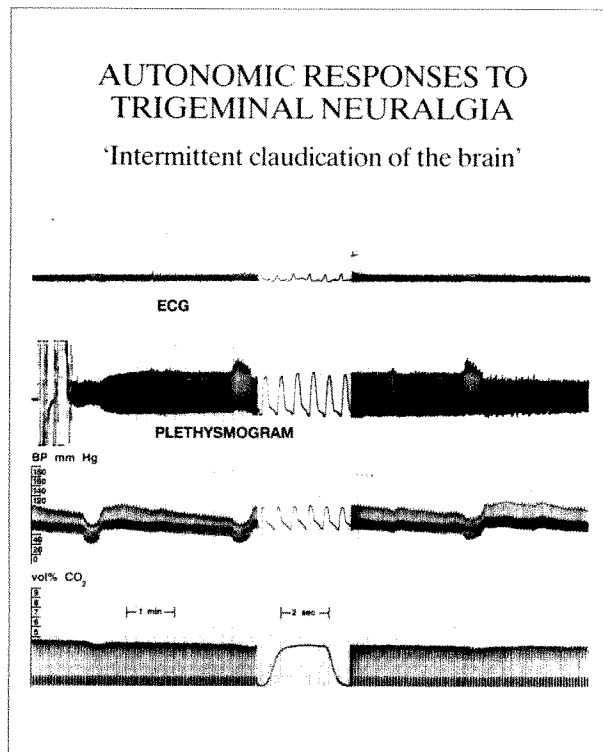


Fig 177

These are the records which were obtained after more fentanyl had been injected intravenously (a total dose of 1 mg had been given). There is no improvement. The plethysmogram is now connected and the oscillations can be seen to increase during each attack. The arrhythmia disappeared.

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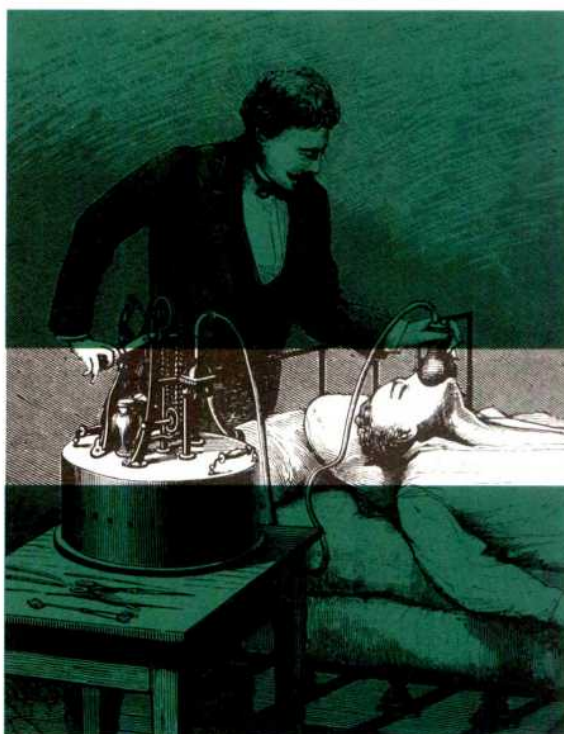
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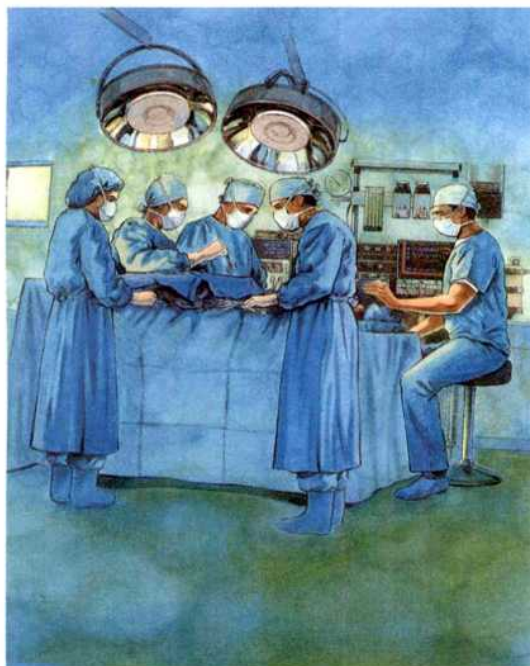
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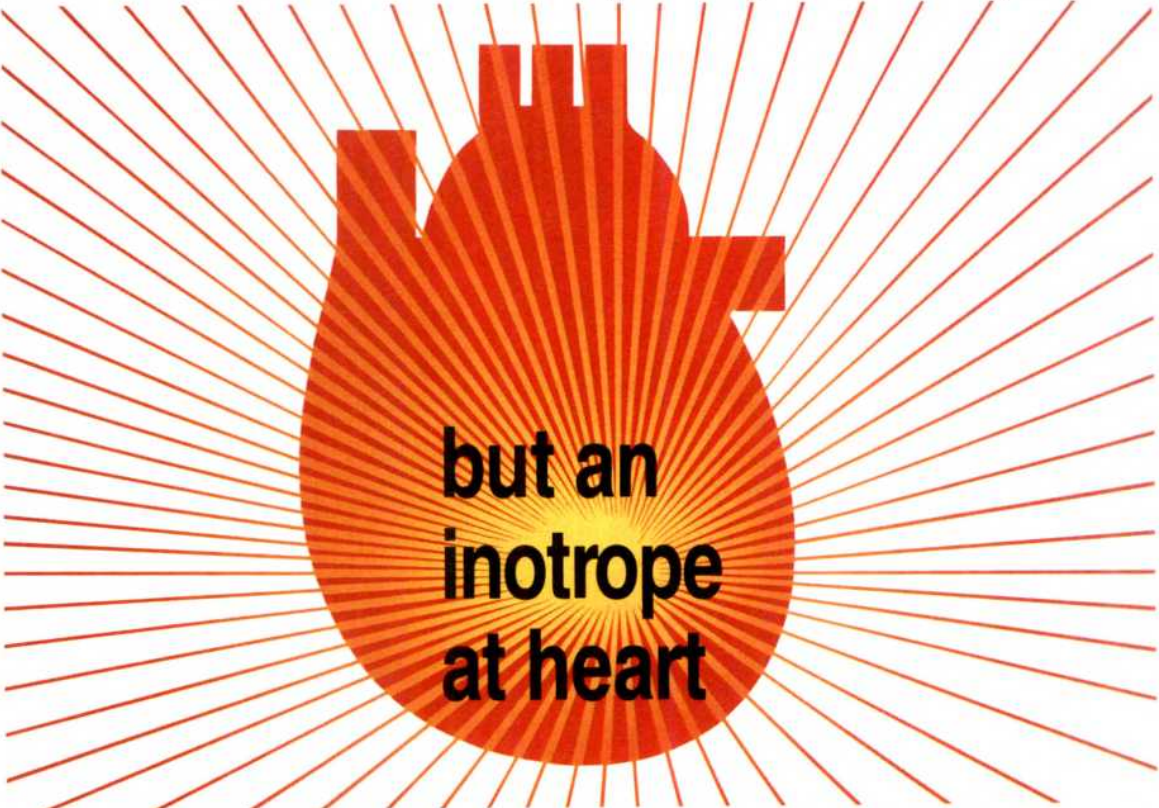
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3. *J Am Coll Cardiol* 1987; **10** (6): 1294-1302
4. *J Am Coll Cardiol* 1986; **8** (2): 413-418
5. *J Am Coll Cardiol* 1987; **9** (4): 711-722
6. *Am J Cardiol* 1987; **59** (15): 1345-1350
7. *Am J Cardiol* 1987; **60** (16): 1329-1333
8. *N Eng J Med* 1983; **309** (13): 748-756
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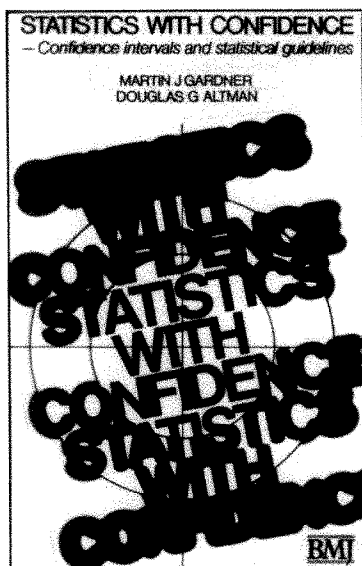
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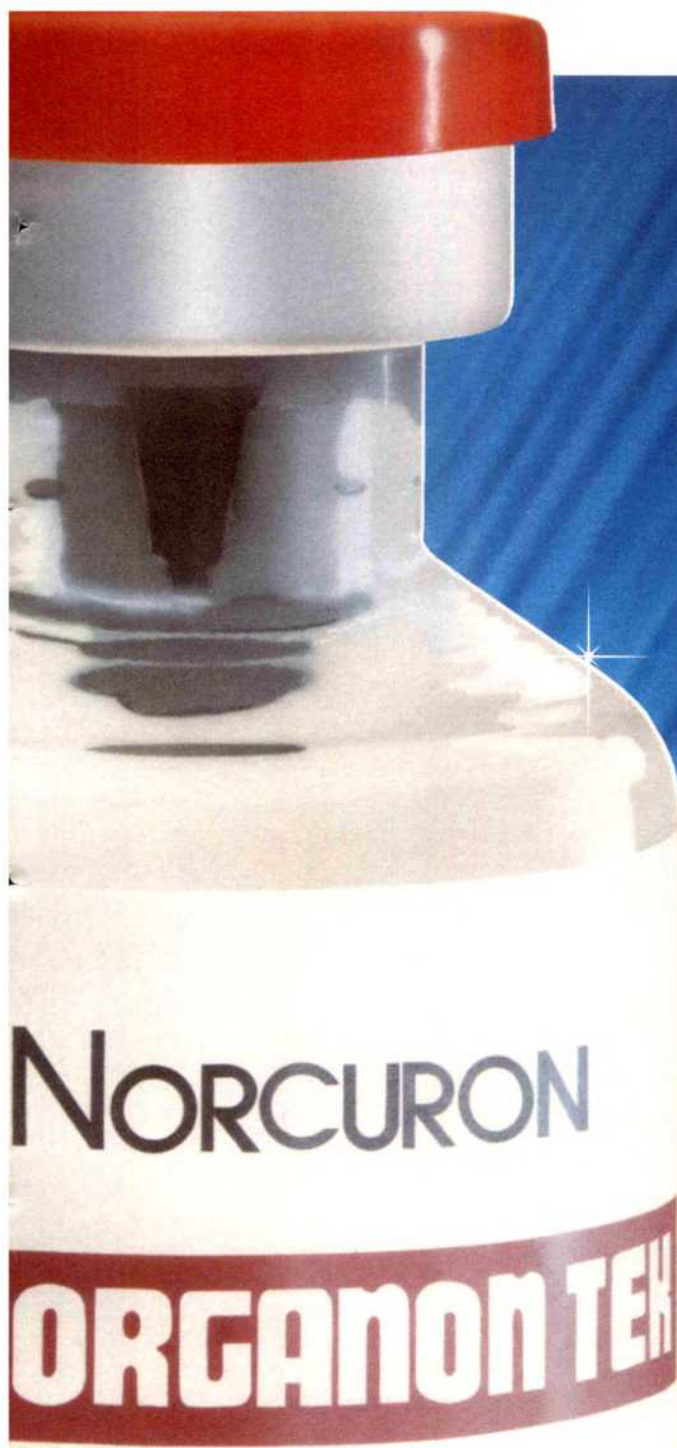


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by the concomitant use of inhalation anaesthetics, eg halothane. In patients with renal insufficiency a slight prolongation of the neuromuscular blockade can be expected after the use of Norcuron. Patients with liver disease or liver insufficiency do not usually require a reduction of the initial dose and some patients may even require a higher dose. Conditions such as electrolyte disturbance, altered pH and dehydration, should if possible be corrected before administration of Norcuron. Norcuron can be used in child birth by Caesarean section without effect on a newly born child. The spontaneous reversal of the neuromuscular blockade caused by Norcuron is rapid. However, when needed, the standard reversal agents eg neostigmine or pyridostigmine, will readily antagonise its neuromuscular effects. **Side effects.** On rare occasions unwanted effects have been reported in association with Norcuron; eg reactions at the site of injection, bronchospasm and in rare instances, anaphylactoid reactions. However, in all instances Norcuron had been administered concomitantly with other drugs and causality is difficult to establish. **Basic NHS Costs.** £65.80 per box of 20 x 10mg vials with 20 x 5ml ampoules W.F.I. **Product Licence No.** 3524/0013.



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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

WHY ARE CHILDREN STARVED?

It is more than 25 years since Watson [1] drew the attention of anaesthetists to the possibility of hypoglycaemia occurring in children fasted in preparation for anaesthesia and surgery.

After the third day of life, hypoglycaemia is defined commonly as a blood concentration of glucose less than $2.2 \text{ mmol litre}^{-1}$ [2]. With values less than this, there is a risk of neurological damage that may be undetected during anaesthesia. Even in the normal awake child, the signs and symptoms of hypoglycaemia are variable, and impaired conscious level or even convulsions may be the first indication.

Since Thomas [3] suggested that the patients most at risk were those younger than 4 yr and of weight less than 15 kg, many other workers have investigated this phenomenon in various groups of patients. A variable incidence of hypoglycaemia has been reported, but in general it has been lower than Thomas suggested; also, younger children have not been shown to be at particular risk. Most cases of hypoglycaemia have occurred in children who have been starved for a period in excess of 10 h.

With changing practice and the movement toward day care units for children requiring minor surgery, new problems have arisen. Because of the lack of supervision before operation and the need for the communication of instructions to parents, there is a tendency to increase the period of preoperative fasting. Logistical considerations may make the time of 09:00 important for the start of the surgical list. However, as many young children go to bed at 19:00, the common instruction of "starve from midnight" implies they are likely to be fasted for 12–14 h, even if they are the first on the operating list. A solution to this problem would be to start day cases later, to allow younger children to receive an early breakfast.

Because of the risk of undetected hypoglycaemia during anaesthesia, many preoperative

feeding schedules have been suggested. Most recommend a period of fasting for 4 h, but some advocate sweet fluids such as apple juice [4] or a clear glucose feed to be given less than 4 h before anticipated induction of anaesthesia. However, the obsessive use of large volumes of fluids in the preoperative period may lead to an increased risk of gastric aspiration during anaesthesia.

The volume and quality of gastric juice, if it is aspirated, which leads to death in man is not known. Work in animals suggests that pulmonary damage may occur if the aspirate volume is greater than 0.4 ml kg^{-1} and the pH less than 2.5 [5]. Other workers [6] have indicated that the volumes required are greater.

The incidence of this aspiration is also difficult to ascertain. In a multicentre study Graft [7] found the incidence of deaths caused by anaesthesia was 3.3 per 1000, and in 28% of the cases aspiration of blood or vomit was a major factor. However, in a more recent study by Olsson [8], the incidence of aspiration (confirmed by x-ray) was 1:4521. In this study of 185358 patients of all age groups, there were only four deaths attributable to inhalation of gastric contents and there was none in the paediatric group. However, aspiration was more common in children and was associated usually with other airway problems.

Premedication has been shown to alter not only the volume of gastric residue, but also the acidity of gastric juice. In a study of different premedication agents, Salen [9] concluded that glycopyrrolate was superior to either atropine or hyoscine in reducing gastric volume. Meakin [10] and co-workers found that the use of trimeprazine orally increased the pH, but temazepam given as an elixir tended to increase the volume of gastric residue. Lerman [11] found that ranitidine 2 mg kg^{-1} alone or in combination with metoclopramide 0.1 mg kg^{-1} significantly reduced gastric volume and increased gastric fluid pH.

The effect of trauma on gastric motility and emptying has been investigated in children by Bricker, McLuckie and Nightingale [12], who concluded that the interval between last oral intake and injury was important in deciding the state of the stomach, but that the sensation of hunger was not indicative of an empty stomach. Some of their patients had high gastric volumes even after 8 h of starvation and they recommended that all children who present for surgery following trauma should have the airway protected during anaesthesia by tracheal intubation.

The use of intraoperative fluids containing glucose has been standard treatment for all children presenting for major surgery because of the risk of dehydration. Glucose-containing fluids are popular because of the assumption that energy requirements are greater and reserves smaller in children. Nuutinen and Hollmen [13] demonstrated that blood concentrations of glucose increase in adults during surgery even if sugar-free fluids are infused. Several factors are responsible for this hyperglycaemic response, including changes in secretion of insulin and the counter-regulating hormones [14]. In this issue of the Journal, Aun and Panesar [15] report that insulin suppression was not observed in children, although why adults and children should differ in this respect is unclear.

Despite many investigations over the years, the problem of identifying patients at risk from hypoglycaemia remains. Most workers agree that it is unlikely to occur in otherwise healthy children unless the period of fasting has been excessive. In this enlightened age, it seems extraordinary that children still present for anaesthesia and surgery after being subjected to a fast in excess of 12 h. It is important for all anaesthetists, particularly those involved in day care units, to ensure that sensible preoperative instructions are given to parents in a way that is easily understood. Nonetheless, while preoperative fluids given orally for up to 4 h before surgery are helpful in ensuring adequate hydration of young patients, it should be remembered that excessive amounts

of sweet fluid may increase the risk of pulmonary aspiration of gastric residue during anaesthesia.

D. C. Miller

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EDITORIAL II

PREDICTING MALIGNANT HYPERTHERMIA

The need to be able to identify, before operation, the patient susceptible to malignant hyperthermia (MH) is obvious, but unfortunately this is not possible at present without the major invasion of a muscle biopsy.

There have been many attempts to "characterize" the MH susceptible (MHS) individual. In the most recent hard-back book on MH, Britt lists "associated muscle, musculoskeletal, skeletal and connective tissue abnormalities" which she claims are present in about 67% of the MHS population [1]. The abnormalities listed include also several diseases such as osteogenesis imperfecta, glycogen storage diseases, various muscular dystrophies, hyperkalaemic periodic paralysis and central core disease. In a clearly argued review of medical associations with MHS, Brownell accepted only the last of these as possibly relevant [2]. The most bizarre of the apparent associations is the so-called King syndrome [3], which includes webbing of the neck and low set ears.

As MH is a comparatively rare complication of anaesthesia, it is uncommon for an individual anaesthetist to see more than a handful of cases in a professional lifetime. Thus we have been dependent largely on anecdotal accounts and case reports for our knowledge of associations—and these are notorious for their fallibility. Perhaps, in this context, the review paper which mentions all and criticizes none performs a disservice because the review itself is often quoted (or misquoted) as a reference source, rather than the original dubious paper, which thereby goes uncriticized.

The paper from Vienna by Werner Hackl and co-authors [4] in this issue of the Journal explores another and intriguing facet of prediction. These authors have compared the presenting features of apparent clinical episodes of MH with the laboratory results of *in vitro* muscle biopsy screening techniques, which follow the well established European MH test procedures. If the assumption is made that the laboratory methods provide the "correct" diagnosis and can confirm or refute whether the clinical episode was MH or not, it is fascinating to read how often the clinician was

wrong, namely in 25 of 61 patients. With increasing awareness of the early signs of MH, it may be anticipated that this proportion of false MH-positive diagnoses will increase because, as the authors state in their introduction, "...the early signs of MH are frequently unspecific and variable."

Although the more information obtained at the time of the clinical episode the greater is the likelihood of a correct diagnosis, the predictive value of the clinical signs themselves varies. It is interesting to find that ventricular arrhythmias and cyanosis, which are non-specific signs, correlated with MHS [4]. The most informative sign was generalized muscular rigidity, yet masseteric muscle spasm, which is presumably causally related, was not helpful in differentiating MHS from MHN (normal) probands. This does not imply that masseteric muscle spasm is not part of the MH syndrome, but that it occurs with equal frequency in both the MHS and the MHN groups studied. However, all these patients were highly selected for study as they had exhibited a clinical episode resembling an acute MH reaction. The presence of a significant degree of masseteric muscle spasm as an sole sign indicates that there is a 0.5 (50%) probability of MH being the cause, a figure which is in close agreement with other reports.

When it was measured, body temperature was a helpful indicator, as were postoperative myoglobinuria and increased concentrations of serum creatine kinase (CK). Yet the predictive value of the most informative signs, when combined, was only 78% specific for MH. This is illustrated well by the similar range of both body temperatures and CK values encountered for both MHS and MHN groups, even though the mean values for both variables for both groups were significantly different ($P < 0.001$ for both).

The authors used a sophisticated mathematical model incorporating logistic regression. As no clear-cut discrimination between MHS and MHN was obtained, this approach cannot be used to help to diagnose MH retrospectively *in an in-*

dividual, although it does confirm that certain clinical signs are associated positively with an MH reaction.

It would be interesting to repeat this study prospectively using more evidence of hypermetabolism, such as oxygen saturation, capnography and blood-gas analysis, in addition to careful note of changes in body temperature. With the continuing introduction of higher levels of technology, perhaps it is not a vain hope that monitoring may improve and permit such a study to be undertaken.

Even if Hackl and co-authors have failed to find a discriminative analysis of clinical signs which is as accurate diagnostically as the results of the currently used *in vitro* muscle tests, they have underlined the signs which are important in making a diagnosis of MH. The anaesthetist has to make a decision on management of a patient without knowledge of CK concentrations or presence of myoglobinuria. His is the more difficult problem of trend analysis, and knowing when and how to act; the present study hardly addresses this.

The genetics of MH is being unravelled at an alarming pace. We know the MH gene is on chromosome 19, and its position is close to the

ryanodine receptor controller gene [5]. It may not be long before there is a specific blood test for MHS which will render muscle studies obsolete; but even a specific test for the MH gene will not aid the anaesthetist faced with a clinical diagnosis. Clinical vigilance, combined with careful monitoring will never be superseded.

F. R. Ellis

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PAEDIATRIC GLUCOSE HOMEOSTASIS DURING ANAESTHESIA

C. S. T. AUN AND N. S. PANESAR

SUMMARY

The perioperative blood glucose regulatory response was compared in 20 healthy children (aged 1-5 yr) presenting for minor surgery and allocated randomly to either a fasted or a glucose group. All children received a milk feed at midnight. The fasted group received no oral intake thereafter, whereas the glucose group received 5% dextrose water 10 ml kg⁻¹ orally about 4 h before operation. The mean plasma glucose concentrations in the two groups were similar before operation and were within normal limits. The pattern of change in the concentrations of plasma glucose, insulin, cortisol, growth hormone and glucagon were also similar between the two groups. Ten percent of patients in the fasted group and 33% in the glucose group had gastric aspirates in excess of 0.4 ml kg⁻¹. The pH of all gastric samples was less than 2.5. The results suggest that healthy preschool children were able to maintain glucose homeostasis after 8 h of fasting. Feeding within 4-6 h before surgery may increase the risk of pulmonary aspiration.

KEY WORDS

Blood: glucose. Surgery: paediatric.

Preoperative hypoglycaemia in children was reported by Watson [1], who found an incidence of 10%, and Thomas [2] who found an incidence of 28%. This may have led to the widely accepted practice of giving sweetened clear oral fluids 4-6 h before operation to small children. However, more recent work [3-6] has demonstrated that children may tolerate a considerable period of starvation (range 2.5-21 h) without evidence of hypoglycaemia. Moreover, hyperglycaemia has been shown to occur commonly in paediatric surgical patients [4, 7-10] and it has been suggested that

this is associated with the endocrine and metabolic stress response [7-10].

The present study was undertaken to examine the effect of preoperative oral glucose administration on perioperative plasma glucose concentrations in children aged 1-5 yr, and the relationship of these glucose concentrations to the pattern of the endocrine response.

PATIENTS AND METHODS

We studied 20 healthy children aged 1-5 yr who presented for routine minor surgery (herniotomy, repair of hydrocele and circumcision) before 09:00. The procedure was approved by the Faculty of Medicine Ethics Committee. Informed consent was obtained from the parents of all the children studied. The patients were allocated randomly to one of two groups, a fasted group and a glucose group. All children received a milk feed at midnight, but those in the glucose group were given in addition a drink of 5% dextrose solution 10 ml kg⁻¹ approximately 4 h before surgery.

All the patients were premedicated orally with trimeprazine 1.5 mg kg⁻¹ (up to a maximum of 30 mg) 3 h before surgery and morphine 0.2 mg kg⁻¹ (up to a maximum of 10 mg) with atropine 0.02 mg kg⁻¹ (up to a maximum of 0.6 mg) by i.m. injection 1 h before surgery.

Anaesthesia was induced with nitrous oxide and halothane in oxygen. A 22-gauge cannula was inserted into a peripheral vein on the dorsum of each hand for collection of blood samples. Tracheal intubation was facilitated with tubocurarine

This article is accompanied by Editorial I.

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0.6 mg kg⁻¹. The lungs were ventilated with 70% nitrous oxide in oxygen using an Ayre's T-piece breathing attachment and a ventilator (Nuffield 200, Penlon Ltd). The fresh gas flow was adjusted to maintain an end-tidal carbon dioxide partial pressure of approximately 4 kPa (Normocap CD 102, Datex Instrumentarium). At the end of surgery, the residual neuromuscular block was antagonized with neostigmine 80 µg kg⁻¹ and atropine 20 µg kg⁻¹. I.v. fluids were not administered during the study. The same anaesthetist and surgeon performed all the procedures, which were comparable for mean duration of surgery (fasted group 19.9 (SD 5.3) min, glucose group 16.7 (SD 6.5) min).

Serial venous blood samples were collected before the operation (after induction of anaesthesia but before tracheal intubation), at the end of the operation, and 30, 60 and 120 min after the operation. The samples were analysed for plasma glucose, cortisol, growth hormone, glucagon and insulin concentrations. Plasma glucose concentrations were assayed enzymatically by the glucose oxidase method using a Beckman Astra-8 analyser, the inter-assay coefficients of variation at 5.4 mmol litre⁻¹ and 17.3 mmol litre⁻¹ being 2.8% and 2.5%, respectively. Hypoglycaemia was defined as a plasma glucose concentration of less than 2.2 mmol litre⁻¹ and hyperglycaemia as more than 11 mmol litre⁻¹ [11]. Samples for measurement of cortisol, growth hormone, glucagon and insulin concentrations were collected in a sample tube containing EDTA and aprotinin (Trasylol, Bayer) as a preservative (1000 units/ml of blood). The samples were placed on ice and centrifuged as soon as possible. The plasma was stored at -70 °C until the hormone concentrations were measured. All hormones were assayed in duplicate using commercial radioimmunoassay kits (cortisol and growth hormone: Diagnostic Products Corporation kits; glucagon: Biodata kits; insulin: Pharmacia kits). The inter-assay coefficients of variation for cortisol were 20% at 43 nmol litre⁻¹, 7.6% at 506 nmol litre⁻¹ and 11.8% at 970 nmol litre⁻¹; those for growth hormone were 12.6% at 4.5 mIU litre⁻¹, 16.3% at 10.9 mIU litre⁻¹ and 21.4% at 25.8 mIU litre⁻¹. The sensitivity of the assay for glucagon was 14.5 ng litre⁻¹ and the inter-assay coefficient of variation was 2.5% at 87.9 ng litre⁻¹; the standard curve was in the range 15–800 ng litre⁻¹. The sensitivity of the insulin assay was 2 mIU litre⁻¹, the coefficient of variation 6.2% at 4.33 mIU litre⁻¹

and the standard curve in the range 3–240 mIU litre⁻¹. The hormone concentrations were corrected for the volume of aprotinin added.

A nasogastric tube was passed into the stomach after induction of anaesthesia and the stomach contents were aspirated, as completely as possible, by moving the tube and gently compressing the abdomen. The volume aspirated was recorded and the pH of the gastric contents was measured with an indicator strip pH 0–6 (Acilit, Merck).

Statistical analysis

Student's *t* test was used to compare the groups. Statistical differences in the concentrations of various analytes were determined by analysis of variance for repeated measures. The Mann-Whitney *U* test was used to test the difference in the volume of gastric aspirate between the two groups. Correlations were determined using the Kendall Rank correlation test. *P* values less than 0.05 were considered significant.

RESULTS

There were no differences between the glucose and fasted groups with respect to the ages and weights of the children: 35.3 (SD 11.2) and 37.7 (14.9) months and 13.7 (2.6) and 14.4 (2.4) kg, respectively.

None of the patients in each group was found to be hypoglycaemic before operation. The mean

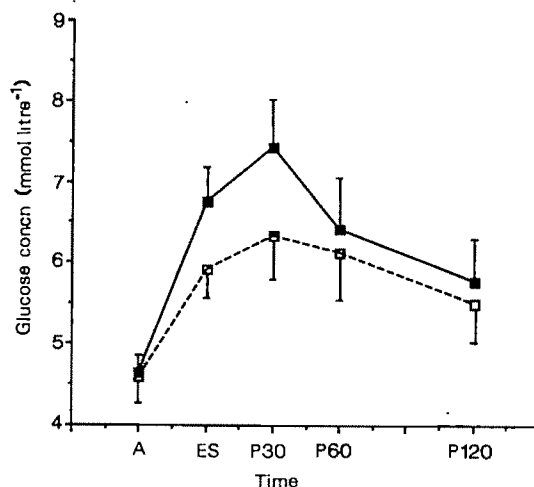


FIG. 1. Changes in plasma concentrations of glucose (mean, SEM) in the glucose (□) and fasted (■) groups before and after surgery. A = After anaesthesia before tracheal intubation; ES = end of surgery; P30 = 30 min after surgery; P60 = 60 min after surgery; P120 = 120 min after surgery.

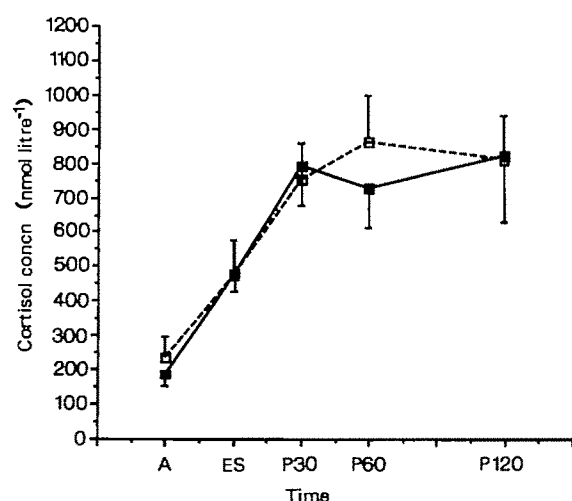


FIG. 2. Changes in plasma concentrations of cortisol (mean, SEM) in the glucose (□) and fasted (■) groups before and after surgery. A = After anaesthesia before tracheal intubation; ES = end of surgery; P30 = 30 min after surgery; P60 = 60 min after surgery; P120 = 120 min after surgery.

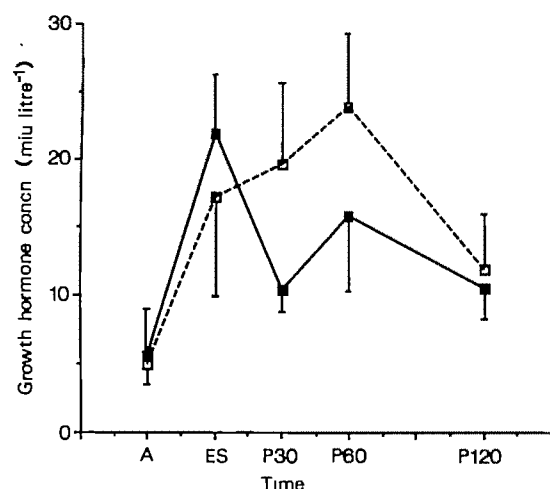


FIG. 3. Changes in plasma concentrations of growth hormone (mean, SEM) in the glucose (□) and fasted (■) groups before and after surgery. A = After anaesthesia before tracheal intubation; ES = end of surgery; P30 = 30 min after surgery; P60 = 60 min after surgery; P120 = 120 min after surgery.

preoperative blood concentration of glucose in the fasted group was 4.64 (SEM 0.21) mmol litre^{-1} and in the glucose group 4.58 (0.36) mmol litre^{-1} (ns) (fig. 1). The mean plasma glucose concentrations increased significantly ($P < 0.01$) following operation and peak values were found 30 min after the end of the operation. Plasma glucose

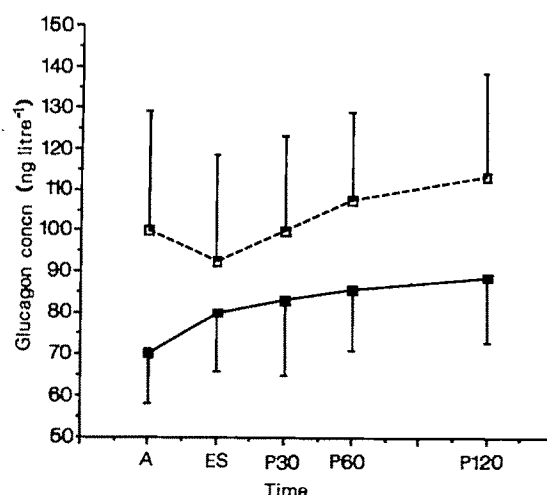


FIG. 4. Changes in plasma concentrations of glucagon (mean, SEM) in the glucose (□) and fasted (■) groups before and after surgery. A = After anaesthesia before tracheal intubation; ES = end of surgery; P30 = 30 min after surgery; P60 = 60 min after surgery; P120 = 120 min after surgery.

values subsequently decreased gradually towards preoperative values.

The mean plasma concentrations of glucose were generally greater in the fasted group, but the differences between the two groups were not significant.

The time course of mean plasma concentrations of cortisol, growth hormone, glucagon and insulin in the two groups are shown in figures 2, 3, 4 and 5, respectively. There were no significant differences between the two groups in the plasma concentrations of any hormone measured before the operation.

All hormone concentrations increased significantly following the operation ($P < 0.01$). Cortisol concentrations increased four-fold by 2 h after operation. Growth hormone, glucagon and insulin values increased to a lesser extent. However, the differences between the two groups were not statistically significant. Only the pattern of change in plasma concentrations of insulin followed that of plasma concentrations of glucose, with a similar trend, reducing towards the preoperative concentrations.

The mean volumes of residual gastric aspirates were 0.53 (range $0-2.9$) ml kg^{-1} and 0.16 (range $0-0.47$) ml kg^{-1} , respectively, for the glucose and fasted group (ns). Gastric aspirate was unobtainable from one patient in the glucose group and three patients in the fasted group. In all cases, the

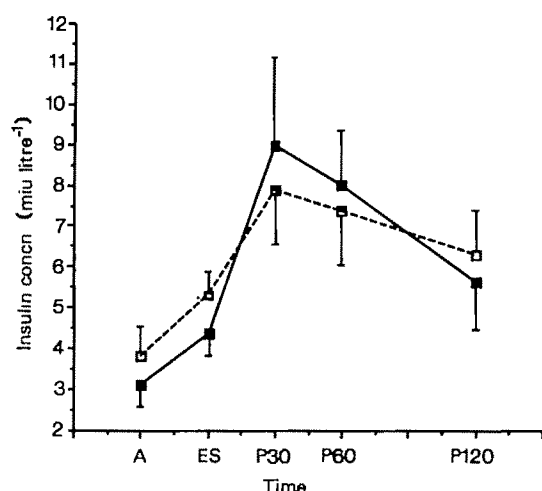


FIG. 5. Changes in plasma concentration of insulin (mean, SEM) in the glucose (□) and fasted (■) groups before and after surgery. A = After anaesthesia before tracheal intubation; ES = end of surgery; P30 = 30 min after surgery; P60 = 60 min after surgery; P120 = 120 min after surgery.

pH of the aspirate was less than 2.5. One patient in the fasted group and three patients in the glucose group had gastric aspirates in excess of 0.4 ml kg⁻¹. One patient in the glucose group had a residual gastric aspirate of 35 ml (2.9 ml kg⁻¹) with a pH of 1.8.

There was a significant correlation between the volume of residual gastric aspirate and age ($P = 0.03$) and body weight ($P = 0.02$) in the fasted group, but no such correlation in the glucose group ($P = 0.91$ and 0.28 , respectively).

There was no vomiting or regurgitation in either group during induction of anaesthesia, operation or recovery.

DISCUSSION

The study has confirmed the ability of healthy children aged 1–5 yr undergoing minor surgical procedures to maintain glucose homeostasis after a reasonable period of fasting (about 8 h) [3–6].

Diurnal variations in the concentrations of circulating hormones were obviated by studying only patients who were scheduled for operation between 08:00 and 09:00. Basal blood samples were collected immediately after an inhalation induction, but before tracheal intubation, as sampling might itself have induced stress and so altered the plasma concentrations of hormone.

None of the preoperative plasma glucose concentrations was indicative of hypoglycaemia in either group, and this suggests that the children were capable of regulating their plasma glucose within normal limits after a reasonable period of fasting. This is in agreement with the findings of other recent studies [3–6]. However, the results in our study may have been affected by trimeprazine syrup given as premedication. This contains sucrose 68% w/v, which is hydrolysed by sucrase in the intestine and absorbed as glucose and fructose. The latter is converted readily to glucose in the liver. The dose used (1.5 mg kg⁻¹) for both groups provided a potential source of glucose in the range 85–170 mg/kg body weight, which is approximately 17–34% of the oral glucose administered (500 mg kg⁻¹) in the glucose group. Our premedication regimen was similar to that of Watson [1]; trimeprazine was given 3 h before anaesthesia. However, 10% of his paediatric patients were hypoglycaemic (< 2.2 mmol litre⁻¹) before operation. Thomas [2] gave trimeprazine 4 h before operation and found a 28% incidence of hypoglycaemia. In our study, there was no preoperative hypoglycaemia and the contribution of the glucose from the trimeprazine to the blood concentration is likely to have been minimal by the time the blood samples were taken. It is difficult to explain the difference between our results and those of Watson and Thomas, as the only variation in method was that we used an inhalation induction with halothane, whereas they used thiopentone.

The plasma concentrations of glucose in the present study may be greater than the true pre-induction concentrations. Van der Walt and Carter [5], have shown that the mean plasma concentration of glucose in arterialized capillary blood increased by 0.5 mmol litre⁻¹ from before to 5 min after induction of anaesthesia. If the plasma concentrations of glucose in this study are adjusted to take account of this change, the values are still not within the hypoglycaemic range.

Hyperglycaemia is the most consistent metabolic effect following surgery [12–14]. The mechanism may be related to concurrent changes in secretion of insulin and counter-regulatory hormones [15]. In adult studies [16–18], an increase in plasma concentration of glucose has been shown during surgery, with suppression of insulin secretion. Suppression was not found in our study, but plasma concentrations of insulin increased after surgery in parallel with plasma glucose. This

finding is similar to that after i.v. infusion of glucose in paediatric patients following surgery [19]. The reason for this difference between adults and children in their response of insulin secretion to surgical stress is not clear.

There was no consistent relationship between the plasma concentration of any of the other counter-regulatory hormones and the changes in plasma glucose. This observation supports the findings of de Fronzo, Sherwin and Felig [15] and Göschke and colleagues [17] that glucose homeostasis is a consequence of the combined effects of insulin, glucagon, growth hormone, cortisol and catecholamine activity. The present study suggests that minor surgical procedures under general anaesthesia do not suppress insulin secretion and activity in paediatric patients and insulin appears to play a predominant rôle in the glucose regulatory process.

The mean plasma concentrations of glucose in the glucose group were, paradoxically, less than those in the fasted group. This may be caused by insulin release following oral glucose and is supported by the insulin concentrations.

A gastric pH < 2.5 and a residual volume > 0.4 ml kg⁻¹ are generally considered to be necessary for pulmonary damage from acid aspiration. Using these criteria, the risk of acid aspiration syndrome in paediatric patients has been reported variously as 3.5% to 76% [5, 20–22]. The risk in our study was 33% in the glucose group and 10% in the fasted group. These observations suggest that the patients in the glucose group were at a greater risk of acid aspiration than those in the fasted group. There was a correlation between the volume of gastric aspirate and the age and weight of the children in the fasted group, but not in the glucose group. This may suggest that glucose has an effect on gastric emptying. In Van der Walt and Carter's study of gastric volume and pH in infants [5], the incidence of patients with both necessary factors was 3.5% when 5% glucose 10 ml kg⁻¹ was given orally 4 h before surgery. All the children were younger than 1 yr, whilst our patients were older, which may account for the difference between the studies. The difference may be related also to the opioid and atropine premedication used in our study. However, Salem and colleagues [23] showed that premedication with morphine and pentobarbitone with or without atropine or hyoscine did not alter gastric volume in children.

In conclusion, this study has confirmed that healthy children aged 1–5 yr undergoing minor surgical procedures were able to maintain their glucose homeostasis after 8 h of fasting. Preoperative feeding within 4–6 h may increase the risk of pulmonary aspiration, especially if an opioid has been used in the premedication. However, there is great variation in individual response and children waiting for surgery should be observed for hypoglycaemia. The findings may not be applicable in infants younger than 1 yr.

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INFLUENCE OF FLUID REGIMENS ON PERIOPERATIVE BLOOD-GLUCOSE CONCENTRATIONS IN NEONATES

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SUMMARY

Blood concentrations of glucose were measured during surgery and during the first 8 h after operation in 30 neonates undergoing major surgery during the first week of life. Fifteen of the neonates were given Ringer-acetate as the only crystalloid peroperative fluid; to the other 15, 10% glucose i.v. was administered during surgery. In the Ringer-acetate group, mean (SD) blood concentration of glucose increased from 3.1 (2.0) to 4.3 (2.4) mmol litre⁻¹ during surgery. The corresponding increase in the glucose-supplemented group was 3.4 (1.5) to 6.3 (2.2) mmol litre⁻¹. In the Ringer-acetate group, peroperative blood concentrations of glucose were found to be low if a preoperative glucose infusion was interrupted at the start of anaesthesia. Hypoglycaemia occurred in both groups, but more often in the group given Ringer-acetate only (3/15 vs 1/15). Hypoglycaemia was found only in neonates less than 48 h of age and during the first 1 h of anaesthesia only. Monitoring of blood concentrations of glucose and adjustment of the glucose infusion appears to be desirable during and after surgery in neonates.

KEY WORDS

Blood: glucose. Fluid balance. Surgery: neonatal.

Low glycogen stores and impaired gluconeogenesis are common problems in newborn infants [1]. A limited period of preoperative starvation and use of glucose-containing solutions during anaesthesia are recommended [2]. In an earlier study, we found no preoperative hypoglycaemia and no correlation between duration of starvation and blood concentrations of glucose in infants

aged 2 weeks-2 yr [3]. No infants given a Ringer-acetate solution only as peroperative fluid became hypoglycaemic. Poor utilization of infused glucose may explain why significantly greater blood concentrations of glucose were found at the end of operation in infants given 2.5% glucose in Ringer's solution. In another study, postoperative hypoglycaemia was not found in neonates younger than 1 week receiving no peroperative glucose [4]. Increased blood glucose concentration associated with peroperative glucose infusion was found immediately after induction of anaesthesia, and especially after surgery, in one study of neonates aged from 1 day to 40 weeks [5], and in another of neonates with a mean postnatal age of 14 days [6].

The aim of the present study was to assess the influence of pre- and peroperative infusion with and without glucose on per- and postoperative blood-glucose concentrations in neonates undergoing surgery during the first week of life.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of the Medical Faculty, University of Gothenburg. Informed consent was obtained from the parents of all infants studied.

Thirty neonates with major congenital defects were studied (table I). They were allocated randomly to receive a peroperative fluid regimen with or without glucose: Ringer-acetate solution only (Ringerdex, Pharmacia AB, Sweden) or Ringer-acetate with 10% glucose solution added to give glucose 0.25-0.30 g (14-

TABLE I. Number of patients, diagnoses, gestational age, birth-weight and age at operation in the four groups. GR = preop. glucose, perop. Ringer-acetate; OR = no preop. i.v. fluid, perop. Ringer-acetate; GG = pre- and perop. glucose; OG = no preop. i.v. fluid, perop. glucose

Diagnosis	Gest. age (weeks)	Birth weight (kg)	Age (h)
Group GR			
Anal atresia	38	1.5	20
Diaphragmatic hernia	39	3.8	25
Diaphragmatic hernia	42	4.3	13
Duodenal atresia	37	2.6	25
Duodenal atresia	39	2.6	19
Oesophageal atresia	38	2.9	9
Oesophageal atresia	39	2.2	18
Oesophageal atresia	42	3.3	11
Omphalocele	37	2.9	21
Pulmonary atresia	40	3.4	49
Group OR			
Abdominal tumour	39	4.0	144
Aortic coarctation	39	3.8	168
Myelomeningocele	36	3.8	6
Myelomeningocele	37	3.5	9
Myelomeningocele	38	3.3	72
Group GG			
Diaphragmatic hernia	38	3.7	7
Hydrocephalus	38	3.3	102
Ileus	40	4.0	76
Myelomeningocele	38	3.5	10
Oesophageal atresia	30	1.3	22
Oesophageal atresia	34	2.2	33
Oesophageal atresia	36	2.4	19
Oesophageal atresia	36	2.7	13
Oesophageal atresia	37	2.8	24
Oesophageal atresia	41	3.5	16
Pulmonary atresia	41	3.8	79
Group OG			
Aortic coarctation	41	3.1	144
Myelomeningocele	36	2.3	6
Myelomeningocele	39	3.7	8
Scrotal tumour	39	4.1	21
Mean	38	3.1	40

17 mmol) kg⁻¹ h⁻¹. Total infusion rate was 15–20 ml kg⁻¹ during the first 1 h followed by 10 ml kg⁻¹ h⁻¹ in both groups. Preoperative i.v. glucose was given to 21 neonates according to our, or the referring hospital's, practice (usually a stepwise increase from 65 to 150 ml kg⁻¹ daily during the first 5 days after birth). Nine neonates had no infusion before anaesthesia; four of these were given breast milk by mouth before operation and were starved for 4 h before operation.

Neonates were classified into four groups: group GR ($n = 10$) had i.v. glucose before and Ringer-acetate during anaesthesia; group OR

($n = 5$) had no preoperative fluid and Ringer-acetate during anaesthesia; group GG ($n = 11$) had i.v. glucose before and i.v. glucose plus Ringer-acetate during anaesthesia; group OG ($n = 4$) had no preoperative fluid and i.v. glucose plus Ringer-acetate during anaesthesia.

All children were taken to the paediatric intensive care unit (ICU) after surgery; depending on their condition, neonates underwent artificial ventilation of the lungs or breathed spontaneously. Peroperative administration of fluid was continued until the neonate arrived in the ICU, when a standardized postoperative fluid infusion of 10% glucose was initiated immediately, at a rate of 2.5–6 ml kg⁻¹ h⁻¹ (65–125 ml kg⁻¹/24 h) depending on postnatal age on the first day after operation. Anaesthesia was standardized and induced with i.v. thiopentone 5 mg kg⁻¹ and maintained with nitrous oxide in oxygen and fentanyl (intermittent doses of 2 µg kg⁻¹, maximum 10 µg kg⁻¹). All children underwent ventilation with a Mapleson D system. Pancuronium or vecuronium 0.1 mg kg⁻¹ was given to facilitate neuromuscular block.

Samples for measurement of blood-glucose concentration and blood-gas tensions were obtained via an arterial cannula before anaesthesia (when available) and during anaesthesia (immediately before the start of surgery and thereafter every 30 min until the end of anaesthesia). In the postoperative period, samples were taken at 1, 4 and 8 h after anaesthesia. Blood-glucose was measured using a glucose-6-phosphate dehydrogenase method (accuracy 5%) [7]. Arterial samples were analysed for pH, Pco₂, standard bicarbonate, Po₂ and arterial saturation using an ABL 2 analyser (Radiometer, Copenhagen).

Data were compared using Student's unpaired t test.

RESULTS

Gestational age was 30–42 weeks, birth weight was between 1.3 and 4.3 kg and patient age at the start of operation was 6–168 h (table I). Duration of anaesthesia was 75–290 min. There were no significant differences in fluid administration between groups except for pre- and peroperative glucose infusion rates ($P < 0.001$) (table II).

In the glucose groups (GG and OG) increasing blood concentrations of glucose occurred throughout anaesthesia, while in the Ringer-acetate groups (GR and OR) only minor changes were observed (fig. 1). From 60 min after the start of

TABLE II. Mean (SEM) pre-, per- and postoperative infusion rates in groups GR (preop. glucose, perop. Ringer-acetate), OR (no preop. i.v. fluid, perop. Ringer-acetate), GG (pre- and perop. glucose), OG (no preop. i.v. fluid, perop. glucose). No significant differences were found except for the pre- and postoperative glucose infusion rates

	Preop. glucose (ml kg ⁻¹ h ⁻¹)	Perop. R.-acetate (ml kg ⁻¹ h ⁻¹)	Perop. glucose (ml kg ⁻¹ h ⁻¹)	Postop. glucose (ml kg ⁻¹ h ⁻¹)
Group GR	2.7 (0.2)	18.9 (1.3)	0	3.3 (0.2)
Group OR	0	17.5 (1.5)	0	3.2 (0.3)
Group GG	3.1 (0.2)	15.2 (1.1)	2.6 (0.2)	3.4 (0.2)
Group OG	0	16.0 (1.5)	2.7 (0.3)	3.2 (0.3)

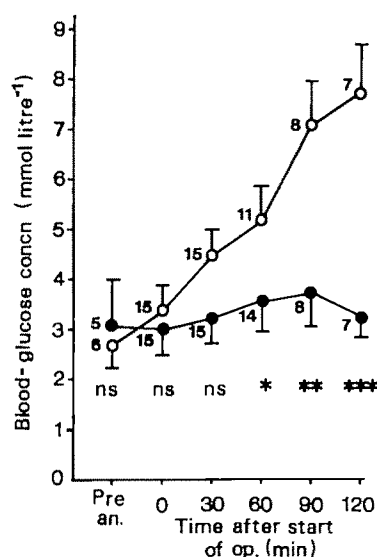


FIG. 1. Mean (SEM) blood-glucose concentrations during anaesthesia and surgery in groups GR and OR (●) and GG and OG (○) (GR = preop. glucose, perop. Ringer-acetate; OR = no preop. i.v. fluid, perop. Ringer-acetate; GG = pre- and perop. glucose; OG = no preop. i.v. fluid, perop. glucose). At each measurement, the number of patients is given. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (t test).

surgery, significantly higher mean concentrations were found in the glucose groups.

Immediately after surgery, the glucose concentrations were greatest in the glucose groups. Four hours after surgery, greater concentrations were found in the groups given only Ringer-acetate during anaesthesia (fig. 2). The highest concentration reached during anaesthesia in neonates receiving glucose during anaesthesia did not differ from the greatest concentration reached after operation for those neonates not receiving glucose during anaesthesia.

Individual blood-glucose values from the four groups are shown in figure 3 (before operation, 30 min after start of surgery, immediately after

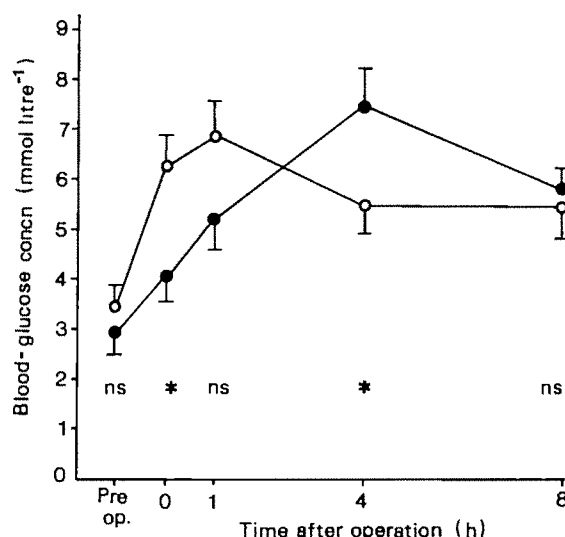


FIG. 2. Mean (SEM) blood-glucose concentrations during the postoperative period in groups GR and OR (●) and GG and OG (○) (groups as in figure 1). * $P < 0.05$ (t test).

surgery, 1, 4 and 8 h after surgery). In three neonates in group GR ($n = 10$), blood concentrations of glucose were occasionally less than 1.7 mmol litre⁻¹ (0.3, 0.7 and 1.2 mmol litre⁻¹). In group GG ($n = 11$) one patient had a blood-glucose concentration less than 1.7 mmol litre⁻¹. These four patients were aged less than 48 h at the start of anaesthesia. Low blood concentrations of glucose occurred during the first 1 h of anaesthesia. Further comparison between the two groups having infusion of glucose before operation (GR with GG) showed significantly lower concentrations for those receiving only peroperative Ringer-acetate at 30 min and immediately after operation ($P = 0.003$, 0.016, respectively). Four hours after operation, mean blood concentration of glucose in group GG was significantly less ($P = 0.048$) than in group GR. A comparison between the groups receiving Ringer-

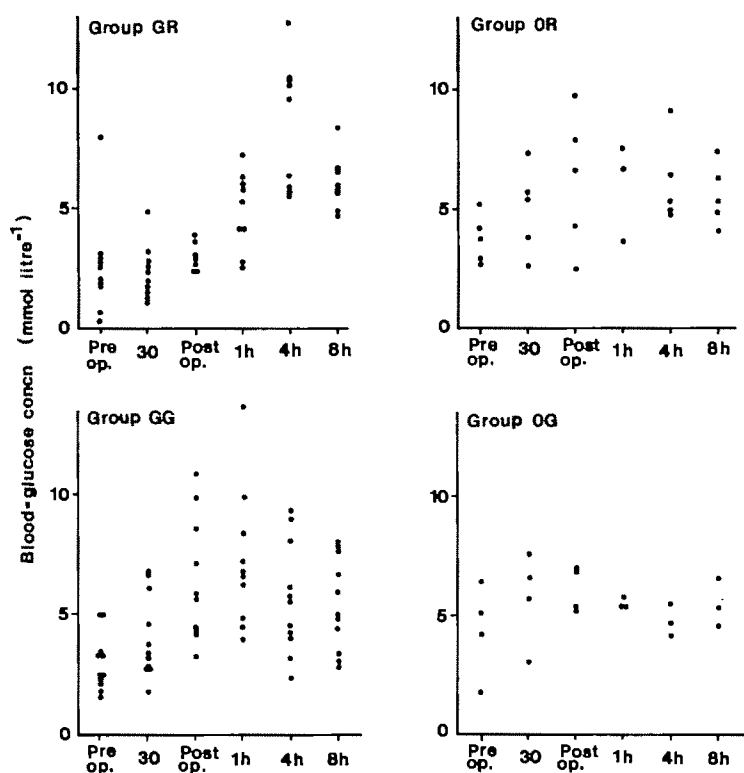


FIG. 3. Individual blood-glucose concentrations before operation (Pre op.), 30 min after start of surgery (30), immediately after operation (Post op.) and 1, 4 and 8 h after anaesthesia, presented separately for the four groups defined in figure 1.

acetate only during operation (GR with OR) revealed significantly lower blood glucose concentrations at 30 min and after operation ($P = 0.0015$, 0.004 , respectively) in the neonates who had glucose infusions during operation. No significant differences were found between the groups which received glucose during the operation (GG and OG).

Mean (SD) standard bicarbonate concentration for all patients was 23.0 (3.8) mmol litre^{-1} before surgery and 22.3 (3.3) mmol litre^{-1} after surgery (not significant). Mean pH was 7.48 (0.15) and 7.44 (0.12) in the same samples (not significant). No significant differences in standard bicarbonate or pH were found when individual or combined groups were compared.

DISCUSSION

Glucose-containing solutions are recommended almost invariably as perioperative fluid for neonatal and paediatric surgery [2, 8–10]. Emphasis

is placed on the low glycogen stores and impaired gluconeogenesis which may lead to undetected hypoglycaemia and neurological damage. The inevitable hyperglycaemia following generous glucose supply during anaesthesia has been discussed less. The low renal threshold for glucose in neonates may cause osmotic diuresis which may influence circulating blood volume. Compared with normoglycaemia, hyperglycaemia with cerebral hypoxia results in accumulation of lactate in the brain. This has been described as an important risk factor for production of neurological damage [11].

Increased blood concentrations of glucose have been found during surgery in both neonates [4, 5, 6, 12], older children [3, 13–15] and in adults [16] exposed to i.v. glucose during surgery and anaesthesia. It is thought that patients of all ages react in a way similar to the sympatho-adrenal response to "stress". The mechanisms for reduced glucose tolerance have been discussed extensively [17]; these include low peripheral

utilization of glucose, increased splanchnic release of glucose and increased peripheral uptake of gluconeogenic substances [18].

Blood-glucose has been measured during and after operation in neonates [4, 6] and the response related to the degree of surgical trauma and to anaesthetic technique. Rebound hypoglycaemia may follow preoperative oral glucose [14] and i.v. glucose loading [19].

In this study, we expected and found an increase in blood concentrations of glucose from the beginning to the end of surgery in neonates receiving peroperative glucose infusion. A less pronounced increase was observed without i.v. infusion of glucose. During the later phases of prolonged anaesthesia without i.v. glucose, blood-glucose did not continue to increase, but there was no decrease. Low glycogen stores and impaired gluconeogenesis may be more important at this stage than earlier during surgery. These results are in contrast with earlier reports [4] of starved, lightly anaesthetized neonates receiving no peroperative infusions. These authors emphasized the use of light anaesthesia and resulting catecholamine release with subsequent metabolic consequences. The neonates in our study were given fentanyl in a dose that may have reduced the stress response at least during superficial procedures.

Our results suggest that the peroperative supply of glucose changed glucose metabolism. With a continuous infusion of glucose in the postoperative phase, normalization of blood-glucose concentrations was found during the first 1 h after operation. In neonates not exposed to glucose until the postoperative period, the increase in that period was similar to the perioperative increase in the glucose group. In both groups, blood-glucose stabilized 8 h after operation. At that time, no difference was found between the groups (fig. 2).

Further separation into groups with respect to preoperative exposure to i.v. glucose demonstrated a significant difference (fig. 3). Hypoglycaemia occurred in the early phase of anaesthesia when a preoperative infusion of glucose was changed to one of Ringer-acetate (GR). Hypoglycaemia occurred also in one patient during peroperative infusion of glucose (GG). All four neonates with hypoglycaemia were younger than 48 h of age at the start of anaesthesia. A similar phenomenon has been noted in the postnatal period when mothers had been given considerable amounts of glucose-containing fluid

for volume replacement associated with extradural anaesthesia during delivery [20].

After the first 30 min of surgery, hypoglycaemia was not observed in any group of neonates. Mean concentrations in the two groups receiving glucose during operation differed also; there were significantly smaller blood concentrations of glucose during surgery in the group given Ringer-acetate (GR) compared with the group given glucose (GG). However, neonates not exposed to glucose before anaesthesia and given only Ringer-acetate (OR) did not differ from the pre- and peroperative glucose group (GG) or from the group receiving glucose only during operation (OG).

The maintenance of blood concentrations of glucose provides energy substrates for the tissues, especially the brain. In newborn infants, hypoglycaemia has been defined as blood-glucose concentrations less than $1.7 \text{ mmol litre}^{-1}$ [21]. To what extent hypoglycaemia might be harmful in this range is not known. In newborn infants, there is rapid transition of the metabolic substrates from mainly glucose during fetal life to free fatty acids [22]. High concentrations of β -hydroxybutyric acid occur in infants and this substance may be used as an energy substrate for the brain also [23]. Rapid mobilization of fat has been seen also in infants not receiving glucose before or during surgery [4].

This study shows that a certain proportion of neonates are at risk of hypoglycaemia during surgery. Hypoglycaemia was observed only in operations performed during the first 48 h of life. It may be avoided in most patients by infusions of glucose-containing solutions during surgery. This may, however, result in hyperglycaemia. Monitoring blood-glucose and continuous adjustment of glucose supply appear to be necessary in order to avoid extensive fluctuations in blood concentrations of glucose.

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PREDICTION OF MALIGNANT HYPERTHERMIA SUSCEPTIBILITY: STATISTICAL EVALUATION OF CLINICAL SIGNS

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SUMMARY

The anaesthetic records of 61 patients who had experienced adverse reactions thought to be malignant hyperthermia (MH) were reviewed retrospectively to evaluate the diagnostic importance of clinical symptoms. Using the in vitro contracture test, 38 (62%) patients were identified as MH susceptible (MHS), the remainder showing normal test results (MHN). Generalized rigidity, ventricular arrhythmias, cyanosis and postoperative myoglobinuria were observed significantly more often in MHS patients. Median values of body temperature and creatine kinase serum concentrations were significantly greater in the MHS group. Masseter spasm and sinus tachycardia were as common in MHS as in MHN individuals. Statistical models using generalized rigidity, ventricular arrhythmias, cyanosis and fever exceeding 38 °C for prediction of MH showed a maximum sensitivity and specificity of 78% and thus are not acceptable for clinical use. For definitive diagnosis of MH, the well established in vitro contracture test remains essential.

KEY WORDS

Hyperthermia: malignant.

anaesthetic reactions in patients who had been screened for MH by muscle biopsy, and to evaluate the diagnostic importance of the symptoms and combinations of symptoms.

PATIENTS AND METHODS

The anaesthetic records of 61 patients (age range 6-60 yr) who had experienced an adverse reaction, thought to be MH, during the decade 1978-88 were reviewed retrospectively together with questionnaires completed by their anaesthetists. Adverse reactions were defined as otherwise unexplained masseter spasm, generalized muscle rigidity, tachycardia (heart rate $> 140 \text{ beat min}^{-1}$), ventricular arrhythmias, cyanotic mottling of the skin, fever, postoperative myoglobinuria and increased creatine kinase (CK).

MH susceptibility was determined by *in vitro* testing of skeletal muscle obtained from a biopsy of the quadriceps femoris muscle. In 31 patients, *in vitro* testing was performed according to the procedure recommended by the European Malignant Hyperthermia Group [3]. Thirty patients had been tested before the introduction of these criteria. Tests were considered positive (MHS) if contractures exceeded 0.25 g when the

Malignant hyperthermia (MH) is a rare inherited disorder, characterized by a potentially fatal hypermetabolic response to various anaesthetic drugs [1, 2]. It is of vital importance to the patient's prognosis that the acute crisis be recognized at an early state. However, this may be difficult, as the early signs of MH are frequently non-specific and variable.

The aim of this study was to analyse the adverse

This article is accompanied by Editorial II.

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specimen was exposed to halothane ≤ 2 vol%. Combined tests using halothane 1 vol% and increasing concentrations of caffeine showed contractures > 0.25 g in all patients at concentrations of caffeine < 1.8 mmol litre⁻¹. Only well defined MH susceptible or MH negative patients were studied; patients with an equivocal test (MHE) were excluded.

Statistical analysis

The average number of adverse signs reported for individual patients in each diagnostic group was compared by the Mann-Whitney test. Associations of dichotomous clinical signs and MH diagnoses were investigated by χ^2 . The diagnostic relevance of each clinical sign alone or in combination with others was investigated by the logistic regression model, the *P* values and the odds ratios being calculated. (The odds ratio is defined as the probability of a patient having a positive MH muscle biopsy, divided by the probability of a negative muscle biopsy. Thus the odds ratio indicates the "relative risk" of being MHS.)

A main aim of the study was to produce a statistical model, which would accurately discriminate prospectively between MHS and MHN. Stepwise multiple logistic regression [4] based on the BMDPLR program [5] was performed. The logistic regression function fitted to our data is defined as:

$$E(y) = 1 / (1 + \exp(-b_0 - b_1 d_1 \dots - b_k d_k))$$

where $E(y)$ = expected probability of MHS; exp = exponential function; b_0 = a constant; b_1 to b_k = coefficients to be estimated; d_1 to d_k = diagnostic factors used by the model (i.e. rigidity, cyanosis, arrhythmia etc.).

By incorporating the estimated coefficients into the above equation, the probability of MHS in an individual patient with given diagnostic factors

may be evaluated. (The diagnostic factors d are entered into the equation as $d = 1$ if the factor is present in a patient, and $d = 0$ if the factor is absent.) Calculated values for $E(y)$ range from 0 to 1.0.

Sensitivity and specificity of the statistical models were judged by the percentage of correctly identified MHS and MHN patients in the sample. True diagnosis was taken to be the result of the *in vitro* contracture test. Two models were tested, one using rigidity, arrhythmias and cyanosis and the other rigidity, cyanosis and pyrexia.

RESULTS

In vitro contracture test

Thirty-eight of 61 patients (62%) were identified as MHS from the *in vitro* contracture test. The rest had normal results.

Distribution of clinical signs

On average, MHS patients had four of the eight clinical signs listed (range 2–8), which was significantly more than the MHN group (average 2, range 1–3; $P < 0.001$). Generalized rigidity, ventricular arrhythmias and cyanosis occurred significantly more often in MHS patients. The same was true for postoperative myoglobinuria (table I), intraoperative temperature and postoperative CK concentrations. However, we were unable to separate MHS patients from MHN, because of the wide scatter of values (table II, figs 1, 2).

Suxamethonium-triggered masseter spasm occurred in 24 of 61 patients. Thirteen (54%) of these were MHS, and 11 (46%) MHN (ns). Sinus tachycardia was of no diagnostic value.

Diagnostic relevance of clinical signs

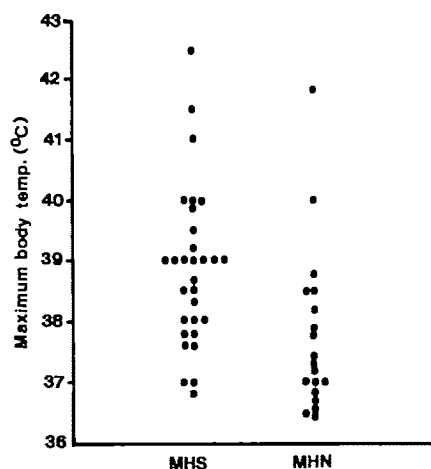
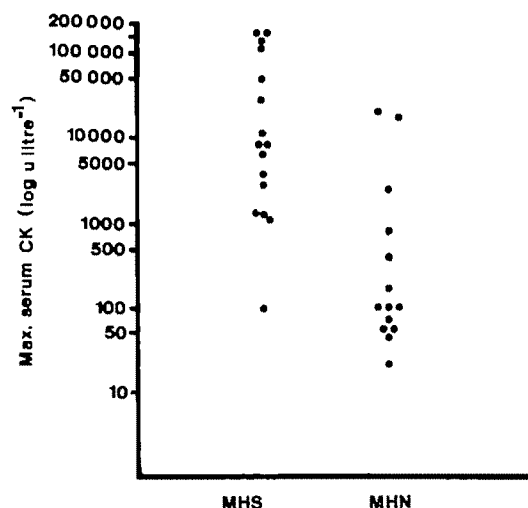
All symptoms which could significantly differentiate between MHS and MHN in 61 patients

TABLE I. Incidence of clinical signs in patients found to be MHS or MHN with *in vitro* testing

Clinical sign	<i>n</i>	MHS incidence <i>n</i> (%)	<i>n</i>	MHN incidence <i>n</i> (%)	<i>P</i>
Masseter spasm	38	13 (34)	23	11 (47)	ns
Generalized rigidity	38	18 (47)	23	1 (5)	0.0001
Tachycardia	38	26 (68)	23	12 (52)	ns
Ventricular arrhythmia	38	15 (39)	23	3 (13)	0.02
Cyanosis	38	23 (60)	23	5 (21)	0.003
Myoglobinuria	17	12 (71)	19	4 (21)	0.003

TABLE II. Quantitative measurements during anaesthesia in MHS and MHN patients

	<i>n</i>	MHS median (range)	<i>n</i>	MHN median (range)	<i>P</i>
Body temperature (°C)	30	39.0 (36.8–42.5)	20	37.7 (36.5–41.8)	0.001
Creatine kinase (u litre ⁻¹)	16	8350 (92–160 000)	14	131 (20–16 900)	0.001

FIG. 1. Distribution of maximum body temperature in MHS (*n* = 30) and MHN (*n* = 20) patients.FIG. 2. Distribution of maximum serum creatine kinase concentrations in MHS (*n* = 16) and MHN (*n* = 14) patients.TABLE III. Diagnostic relevance of clinical signs occurring alone or in combination (expressed as odds ratio; *n* = 61): total number of patients (*n*), and number of MHS patients (*n* (MHS)) in whom the clinical sign was absent and present

Clinical sign	<i>n</i>	<i>n</i> (MHS)	Univariate analysis		Multiple regression	
			Odds ratio	<i>P</i>	Odds ratio	<i>P</i>
Generalized rigidity						
Absent	42	20	19.8	0.0001	26.4	0.0001
Present	19	18				
Arrhythmia						
Absent	43	23	4.3	0.036	6.2	0.024
Present	18	15				
Cyanosis						
Absent	33	15	5.5	0.005	5.4	0.018
Present	28	23				

were of significant diagnostic value when evaluated alone (univariate analysis) (table III) or when corrected for each other (multiple regression analysis) (table III). In both cases generalized rigidity proved to be of greater diagnostic value (odds ratios 19.8 and 26.4, respectively) than

cyanosis (odds ratios 5.5 and 5.4, respectively) and ventricular arrhythmias (odds ratios 4.3 and 6.2, respectively).

An analogous analysis was undertaken in 50 patients, for whom the maximum increase in body temperature was available from the anaesthetic

TABLE IV. Diagnostic relevance of clinical signs occurring alone or in combination (expressed as odds ratio; $n = 50$): total number of patients (n), and number of MHS patients (n (MHS)) in whom the clinical sign was absent and present

Clinical sign	n	n (MHS)	Univariate analysis		Multiple regression	
			Odds ratio	P	Odds ratio	P
Generalized rigidity						
Absent	36	17	14.6	0.014	14.9	0.021
Present	14	13				
Cyanosis						
Absent	27	11	6.9	0.004	7.0	0.012
Present	23	19				
Body temp. $> 38.0^{\circ}\text{C}$						
Absent	24	10	4.7	0.013	4.2	0.05
Present	26	20				

TABLE V. Regression coefficients for the clinical signs used in determining the prognostic index ($E(y)$). See text for details

Diagnostic factor	Model 1	Model 2
	$b_0 \dots -1.313$	$b_0 \dots -1.618$
d_1 generalized rigidity	$b_1 \dots 3.275$	$b_1 \dots 2.696$
d_2 cyanosis	$b_2 \dots 1.683$	$b_2 \dots 1.952$
d_3 ventricular arrhythmia	$b_3 \dots 1.828$	—
d_4 temperature $> 38^{\circ}\text{C}$	—	$b_3 \dots 1.445$

records. An increase to greater than 38°C , generalized rigidity, cyanosis and ventricular arrhythmias were used as variables. In this group of patients, generalized rigidity, cyanosis and

pyrexia were of significant diagnostic importance in both the univariate and the multiple regression analysis (table IV). Ventricular arrhythmia was not significant and thus was eliminated by the logistic regression model. The odds ratios listed in table IV reveal that generalized rigidity was again of most diagnostic value.

Predictive value of symptom combinations

The regression coefficients b_0 to b_3 for the signs generalized rigidity, arrhythmias, cyanosis and pyrexia are shown in table V. The percentage of correctly identified MHS and MHN patients of the sample for various values of $E(y)$ are shown in

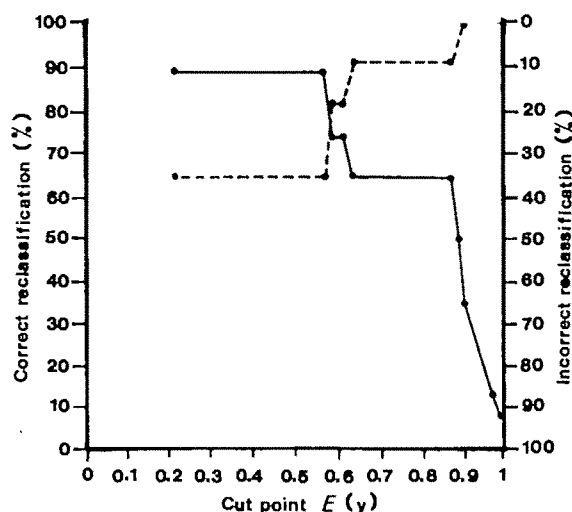


FIG. 3. Percentage of patients ($\bullet$ = MHS; $\circ$ = MHN) correctly classified at various values of $E(y)$ using models 1. See text for details.

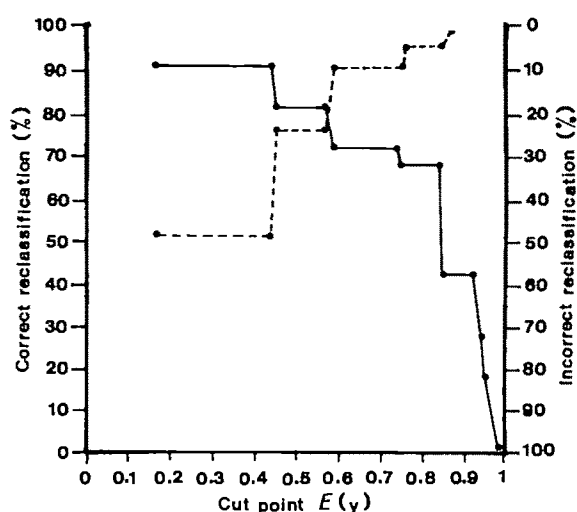


FIG. 4. Percentage of patients ($\bullet$ = MHS; $\circ$ = MHN) correctly classified at various values of $E(y)$ using model 2. See text for details.

figures 3 and 4. Sensitivity and specificity of this procedure was strongly influenced by the choice of the value of $E(y)$ for classifying a patient as MHS or MHN. No value of $E(y)$ enabled precise separation of the two groups (figs 3, 4). In both models the optimum value for $E(y)$ was 0.57, giving correct classification in 78 % of subjects.

DISCUSSION

The data for the study were gathered from hospitals from the whole of Austria. While the clinical observation of symptoms was generally satisfactory, quantitative observations often fell short of requirements and had to be omitted from the calculations. This applied particularly to blood-gas analyses, serum electrolyte concentrations and estimations of expiratory PCO_2 . The aim of the study was to gain a maximum of information from a small number of patients, as MH is a rare condition. Therefore, logistic regression analysis was used for evaluation. However, extensive model analyses, particularly regarding symptom interactions, were not carried out, because of the limited data regarding postoperative changes in CK concentration, and myoglobinuria.

Generalized rigidity proved to be the most specific sign, confirming the results of Larach and co-workers [6], who observed the sign in 76 % of verified crises. Larach's patients were children, which may explain the different incidence. Her diagnostic value of generalized rigidity defined by an odds ratio of 18.9 is comparable to ours, which was 19.8 (table III).

In contrast with Larach and co-workers, we demonstrated that ventricular arrhythmias, cyanosis and a body temperature $> 38^\circ\text{C}$ were also of significant diagnostic importance. The prevalence of ventricular arrhythmia in our MHS patients was greater than in Larach's group (39 % compared with 29 %), but less than in the studies of Ellis, Cain and Harriman (75 %) [7] and Britt (90 %) [1]. The prevalence of cyanosis was comparable between the studies. Pyrexia was not a constant early sign of MH, which is in accord with other studies [2, 6]. An intraoperative increase of body temperature to more than 38°C was of significant diagnostic value in our patients, and was of more value than the occurrence of ventricular arrhythmias.

Masseter spasm was related to MHS in 54 %,

confirming previous studies [6, 8, 9]. It was the only adverse sign in six (26 %) MHN patients, but was never the sole sign in MHS patients. Ellis and Halsall reported "suxamethonium spasm" as the sole clinical sign in seven (0.6 %) of 115 proven MHS patients [9]. Thus no definitive conclusion can be derived from these findings and any patient developing masseter spasm should be assumed to be potentially at risk from MH.

The model for prediction of MH enabled a correct classification of MHS or MHN in only 78 % of patients. Analogous calculations using the signs generalized rigidity, ventricular arrhythmia, cyanosis, body temperature and CK values improved the model's maximum sensitivity and specificity to 87 %. However, the sample size (30 patients) was smaller than in models 1 and 2. As the MH crisis is a potentially fatal event, our model is not acceptable for prospective clinical use.

In conclusion, none of the clinical symptoms can be regarded as specific signs of MH. Prediction of MH susceptibility by clinical signs is limited to a few fulminant cases. The *in vitro* contracture tests remain essential for confirming or rejecting the diagnosis of MH in less pronounced or abortive cases.

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POSTOPERATIVE ANALGESIA AFTER PAEDIATRIC ORCHIDOPEXY: EVALUATION OF A BUPIVACAINE-MORPHINE MIXTURE†

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SUMMARY

The value of combining morphine with bupivacaine for caudal analgesia was investigated. Thirty children, undergoing orchidopexy, received a caudal block of 0.125% bupivacaine with or without morphine 0.05 mg kg⁻¹. Analgesia, side-effects, ventilatory frequency and oxygen saturation (Sa_{O₂}) were recorded after operation. None of the 15 patients receiving the bupivacaine-morphine mixture required post-operative opioids, whereas eight of 15 patients receiving bupivacaine alone needed additional opioid analgesia. The incidence of side effects after surgery was similar for the two groups and there was no detectable difference in ventilatory frequency or Sa_{O₂}.

KEY WORDS

Anaesthetic techniques: caudal. Anaesthesia: paediatric. Anaesthetics local: bupivacaine. Analgesics: morphine. Pain: postoperative.

Caudal injections of bupivacaine are used routinely to provide analgesia after lower abdominal and urogenital surgery in children [1, 2]. However, the analgesic effects of the caudal block often terminate early in the postoperative period and supplementary i.m. injections of opioids are required [3]. Recent studies [4-7] have reported the use of caudal morphine in children for postoperative analgesia with doses varying from 0.03 to 0.1 mg kg⁻¹. The greater doses provided longer-lasting analgesia than bupivacaine, but side-effects (nausea, vomiting, urinary retention and pruritus) were common and a case of ventilatory depression in a 2-yr-old child after a 0.1-mg kg⁻¹ injection of caudal morphine has

been reported [8]. Smaller doses have few side-effects, but are short-acting and unreliable. We therefore compared the analgesic efficacy and side-effects of a combination of bupivacaine and morphine with bupivacaine alone.

PATIENTS AND METHODS

After approval from the Hospital Ethics Committee and informed parental consent, we studied 30 children, aged 9 months to 11 yr, undergoing elective orchidopexy. The children were otherwise healthy (ASA status I or II), fasted and unpremedicated. EMLA cream was applied to both hands at least 90 min before surgery; anaesthesia was induced with thiopentone and atropine and maintained with nitrous oxide, oxygen and enflurane given by face mask. After induction of anaesthesia and before surgery, patients were placed in the left lateral position and a 20-gauge needle inserted into the caudal space through the sacrococcygeal ligament using an aseptic technique. If no blood or CSF was aspirated, a 0.75-ml kg⁻¹ caudal injection of either 0.125% bupivacaine or 0.125% bupivacaine with morphine 0.05 mg kg⁻¹ was given by random allocation, in each case the composition being

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known only to one person who was then excluded from further contact with the patient.

After surgery, the patients were transferred to a recovery area and observed for 1 h before returning to the general ward. The time from induction of anaesthesia to the end of surgery, and the time from the end of surgery to spontaneous opening of the eyes were noted. The quality of analgesia was assessed hourly for the first 6 h and then every 3 h for 20 h, by trained observers who remained unaware of the treatment given. The assessments were based on an observational scoring system modified from Hannallah and colleagues [9], using five criteria: crying, movement, agitation, posture and localization of pain. Each criterion scored 0–2 to give a summed score of 0–10. A total score less than 4 was taken as an indication of adequate analgesia, based on previous experience with this technique [3]. Nalbuphine 0.3 mg kg^{-1} i.m. or oral paracetamol 15 mg kg^{-1} was given by the observers as they felt appropriate. Postoperative recordings included the times of administration of nalbuphine and paracetamol, the time to first micturition after surgery and the incidence of side effects such as nausea, vomiting and pruritis. Patients were discharged home the following morning, provided they had passed urine and were fully mobile without pain.

The nursing staff recorded ventilatory frequency every 30 min for the first 6 h after operation and then hourly for a further 6 h. In addition, ventilatory frequency and oxygen saturation were recorded using a Hewlett-Packard ECG/impedance pneumography unit and a Novo-

TABLE I. Patient data and duration of anaesthesia and surgery (median and ranges)

	Bupivacaine alone	Bupivacaine-morphine
Age (yr)	5.2 (1.2–10.5)	5.0 (0.9–10.6)
Weight (kg)	16.9 (11.5–28.0)	17.0 (9.0–42.0)
Duration of procedure (min)	45 (15–60)	45 (20–60)

metrix pulse oximeter. The data were stored on a BBC microcomputer for subsequent analysis using an established data compression technique [10].

Statistical significance was determined with the Fisher exact test or chi-square analysis with Yates' correction where appropriate for nominal data, the Mann-Whitney *U* test for non-parametric data and Student's *t* test for parametric data. The mean and the variance of the computerized ventilatory data were compared using the *Z* and *F* test [11].

RESULTS

There were 15 patients in each treatment group; mean ages and weights and duration of anaesthesia and surgery were similar for both groups (table I).

There were significant differences between the groups in the requirement for postoperative i.m. analgesia (fig. 1). Three patients in the bupivacaine alone group required nalbuphine during the first 1 h after operation, and the cumulative

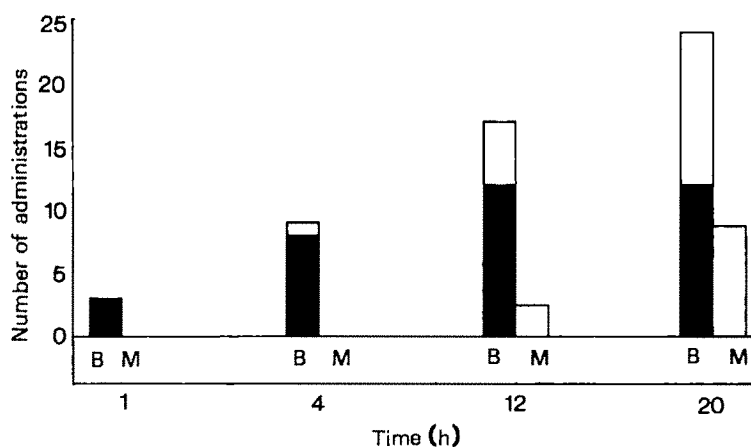


FIG. 1. Postoperative analgesic requirements for bupivacaine alone (B) and bupivacaine-morphine (M). ■ = Injected nalbuphine; □ = oral paracetamol.

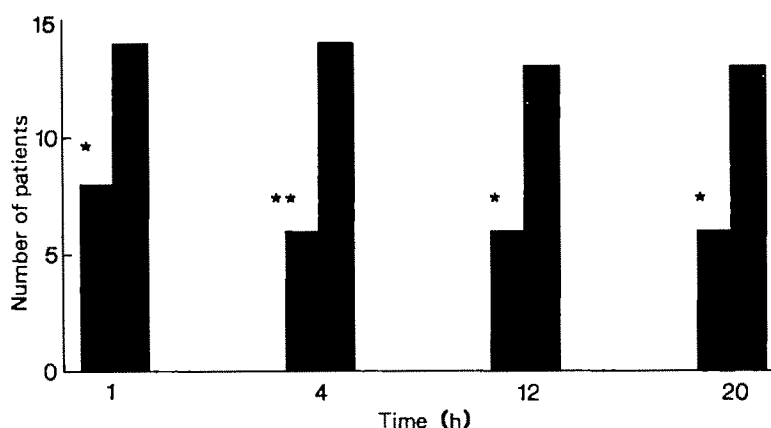


FIG. 2. Number of patients remaining pain free after surgery without requiring i.m. nalbuphine.

* $P < 0.05$; ** $P < 0.01$. ■ = Bupivacaine alone; ■ = bupivacaine-morphine.

TABLE II. Postoperative recovery and incidence of side effects

	Bupivacaine alone	Bupivacaine-morphine
Time to awakening (min) (median (range))	15 (5-30)	10 (5-35)
Nausea/vomiting	5	6
Persistent vomiting	2	2
Pruritis	0	2
Time to micturition (h) (mean (SD))	8.3 (3.1)	8.3 (3.4)

number of patients given nalbuphine over 20 h was 8 for the bupivacaine alone group and 0 for the bupivacaine and morphine group. This difference in analgesic requirement was significant ($P < 0.05$). In addition, three patients required a second injection of nalbuphine during the study period, bringing the total number of administrations of nalbuphine to 11 for the bupivacaine alone group compared with none for the combined bupivacaine and morphine group. Paracetamol requirements were similar for the two groups: after 20 h, 10 patients in the bupivacaine alone group and seven in the bupivacaine and morphine group had received oral paracetamol. Two patients in the bupivacaine alone group were given additional doses of paracetamol.

Correspondingly, fewer patients in the bupivacaine alone group maintained adequate postoperative analgesia (a pain score of less than 4) in the absence of nalbuphine (fig. 2). After 20 h, only six of the 15 patients in the bupivacaine alone group had received adequate analgesia, com-

pared with 13 for the bupivacaine and morphine group.

The addition of morphine to the caudal block did not delay recovery from anaesthesia and the mean time to the first micturition after surgery was similar for both groups (table II). Five patients in the bupivacaine alone group and six in the bupivacaine and morphine group had episodes of vomiting or retching. Two patients in both groups had three or more episodes of vomiting in the postoperative period. Nasal pruritus occurred in two patients, both in the bupivacaine and morphine group, but this did not distress the patients.

Ventilatory frequencies observed by the nursing staff for the first 12 h after operation were similar for both groups (fig. 3). The recorded ventilatory data derived from impedance measurements were analysed separately as data from the first 1 h and data from 1 h to 12 h, because it was felt that ventilatory depression caused by systemic absorption of morphine would be most noticeable during the first hour. The data for an individual patient were extracted as the time spent at each ventilatory frequency and summed for all the patients in the group to derive the total time at each frequency. Absolute values were converted into percentages to allow comparison between groups. We were unable to detect differences in ventilation, and mean ventilatory frequency and variance in the population were similar for the two groups, both in the first 1 h and from 1 h to 12 h (fig. 4).

Patients were given oxygen by face mask for a variable period in the recovery ward, and oxygen

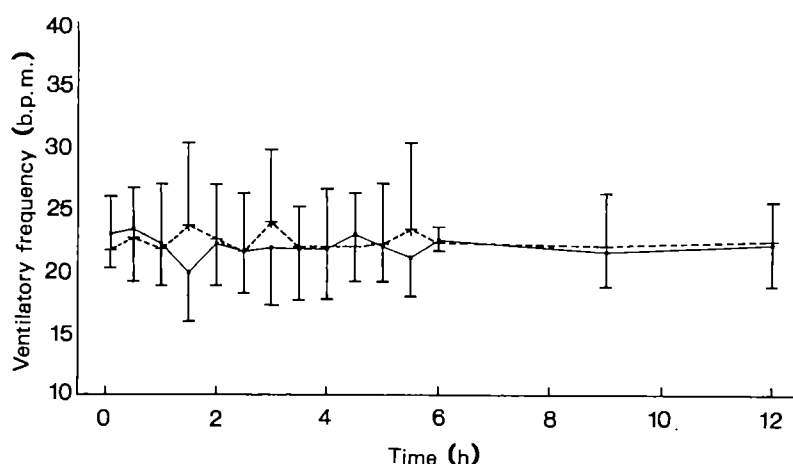


FIG. 3. Observed ventilatory frequency over the first 12 h after operation (means, SD).
— = Bupivacaine alone; --- = bupivacaine-morphine.

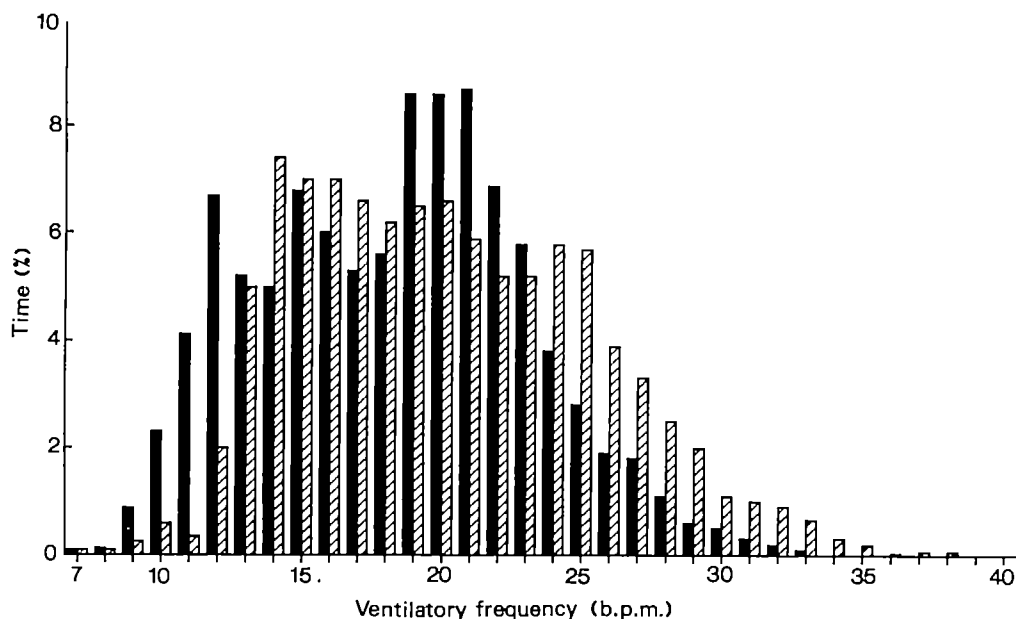


FIG. 4. Ventilatory frequency from 1 h to 12 h after operation recorded from impedance monitor.
■ = Bupivacaine alone; ▨ = bupivacaine-morphine.

saturation data were therefore not stored in the first 1 h. The median oxygen saturation for 1–12 h for each patient was extracted and combined for each treatment group to give a mean and standard deviation of the median values. The averaged median value of oxygen saturation for the bupivacaine alone group was slightly higher than the bupivacaine and morphine group, with a value of 98.0% (SD 1.6) compared with 96.7% (SD 2.0), but the difference was not statistically significant and an oxygen saturation of less than 85% was

not recorded in any patient. Some traces showed isolated decreases in saturation to less than 90%, but these were transient and not associated with a particular treatment group.

DISCUSSION

This study demonstrates that the addition of morphine 0.05 mg kg⁻¹ to a 0.125% solution of bupivacaine improved significantly both quality and duration of pain relief after orchidopexy

without increasing side effects noticeably. The presence of morphine in the caudal space did not result in any detectable differences in oxygen saturation or ventilatory frequency, although more sophisticated tests such as the ventilatory response to carbon dioxide may show depression of ventilatory drive after extradural opioids [12]. Minor changes in the carbon dioxide-ventilation response curve are of little clinical significance and probably unrelated to the sudden onset of severe ventilatory depression that has been reported occasionally after extradural morphine in adults. Ventilatory monitoring or close observation is needed immediately after caudal administration of morphine, but it is important to set a time limit to the risk period for ventilatory depression. The estimate must be conservative, but take into account available clinical experience. Ventilatory depression occurring more than 6 h after extradural administration is extremely rare [13] and associated with factors that include large and repeated doses of extradural morphine, additional opioid or sedative drugs, patients with significant systemic disease (ASA III/IV) and rostral delivery of the opioid. The administration of a very small dose of morphine at the caudal limits of the extradural space as a single injection under light general anaesthesia without additional sedative or opioid drugs minimizes the above risk factors. We believe, therefore, that when a single dose technique is used for caudal morphine, special monitoring can be discontinued safely after 6 h, provided the patient has shown no signs of excessive sedation within the preceeding 6 h, and that the patient remains under nursing supervision for a total of 12 h after the injection. If additional doses of morphine are given either caudally or systemically within the first 12 h, monitoring should be continued accordingly.

Caudal blocks with bupivacaine alone can provide excellent analgesia in the early postoperative period after orchidopexy, but may allow the false impression that the patient will remain pain free thereafter. Longer inpatient studies, lasting 8 h or more, have shown that, as the caudal block wears off, systemic opioid analgesia is required often [3, 14]. In this present study, eight of 15 patients (53%) receiving 0.125% bupivacaine alone required supplementary i.m. analgesia in the postoperative period. These results are similar to a previous study on orchidopexy [14] in which, despite the use of higher concentrations and volumes of bupivacaine, 53%

of patients required further analgesia. This confirms the view that increasing the concentration of bupivacaine to more than 0.125% [3] or the volume to more than 0.75 ml kg⁻¹ [15] offers little therapeutic advantage for this particular procedure.

Morphine given by the caudal route is not merely an exotic alternative to the i.m. route. Systemic uptake of caudal morphine is rapid and provides analgesia in the immediate operative and postoperative period. However, 1 h after caudal injection of morphine 0.05 mg kg⁻¹, plasma concentration is less than 12 ng ml⁻¹ [16], and is unlikely to be associated with significant analgesia. Therefore, the prolonged postoperative pain relief following caudal morphine is caused probably by a specific action on the spinal cord.

Caudal morphine may offer analgesic advantages over bupivacaine alone, but the incidence of side effects increases in parallel with both the duration of analgesia and the dose of morphine [7]. In this study we were unable to detect an increase in side-effects caused by addition of morphine. The overall incidence of vomiting in this study (11 of 30 (36%)) seems high, but is consistent with previous postoperative studies on orchidopexy in children. The children were not encouraged actively into attempts at micturition. A more pressurized approach might have resulted in differences between the groups, but we felt that passive observation was clinically more realistic.

Caudal morphine has not been established as a routine technique in paediatric anaesthesia and this may reflect partly the fear of potentially serious side effects. Minimizing the dose of morphine to provide effective analgesia without side effects is therefore an important goal in the development of the technique. Local anaesthetics may potentiate the analgesic effects of spinal morphine, resulting in improved analgesia at lower doses. A recent study in mice [17] has shown that addition of bupivacaine to morphine increases the intensity of antinociception with a time course similar to that of morphine alone, but of greater potency and reliability. In addition, doses of morphine or bupivacaine that on their own have little or no antinociception may produce an enhanced effect when combined.

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PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER INTERCOSTAL NERVE BLOCK IN PATIENTS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

A. BODENHAM AND G. R. PARK

SUMMARY

Bilateral intercostal nerve blocks were performed on 12 occasions in 11 patients after liver transplantation. Group 1 (six patients) received bupivacaine 2 mg kg⁻¹ on one occasion; in group 2 (five patients) bupivacaine 2 mg kg⁻¹ with adrenaline 1:200 000 was injected on two occasions separated by 6 h. Arterial blood was sampled repeatedly and analysed for total bupivacaine concentrations by high performance liquid chromatography (HPLC). Six patients had bupivacaine concentrations within the putative toxic threshold of 2-4 µg ml⁻¹. The use of adrenaline-containing solutions neither slowed absorption reliably nor decreased peak concentrations of bupivacaine. Cumulation of bupivacaine occurred in group 2. No patient had adverse effects attributable to the bupivacaine.

KEY WORDS

Anaesthetics local: bupivacaine, plasma concentration. Anaesthetic techniques: intercostal.

Intercostal nerve blocks are an effective method of providing analgesia following both thoracic and abdominal incisions. This technique has been used successfully at this centre for several years to provide analgesia and reduce opioid requirements in patients after liver transplantation. There are, however, only limited data on the use of local anaesthetic agents in patients with liver disease. Patients with severe liver disease develop portal hypertension and extensive collateral vessel formation. The effects of these enlarged vessels on the rate of drug absorption is not known. In addition, the ability of the recently transplanted liver to metabolize drugs has not been established.

The long duration of action of bupivacaine makes it the drug of choice for intercostal nerve

block. We therefore measured total plasma concentrations of bupivacaine after intercostal blocks in patients who had undergone liver transplantation. Two groups were studied using bupivacaine with and without adrenaline, and after single and repeated injections.

PATIENTS AND METHODS

Eleven patients who required analgesia on the first or second day after liver transplantation were allocated consecutively to two groups:

Group 1 comprised six patients given a single set of bilateral intercostal nerve blocks using plain bupivacaine 2 mg kg⁻¹.

Group 2 consisted of six studies in five patients having two sets of bilateral intercostal nerve blocks separated by 6 h using bupivacaine with adrenaline 1:200 000 (2 mg kg⁻¹ for each set of injections). One patient was studied on two occasions, 4 months apart, after her first and second liver transplant.

Approval was obtained for the study from the hospital Ethics Committee and written informed consent was obtained before operation from each patient. The intercostal nerve blocks were performed when the patient was ready for tracheal extubation, usually on the first day after operation. A baseline blood sample was withdrawn from a radial arterial cannula, inserted previously for other purposes. Bilateral intercostal nerve blocks (T5-T10) were performed using a standard technique [1] by the same operator (A.B.). In

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smaller, wasted patients the dose of bupivacaine was made up to a minimum volume of 30 ml allowing an adequate volume of solution. Arterial blood (5 ml) was sampled at 5, 10, 15, 30, 60, 120, 240 and 480 min after injection of bupivacaine. In group 2 an extra sample was taken at 2.5 min and the final sample taken at 360 min, immediately before the intercostal blocks were repeated. Blood was collected in tubes containing lithium heparin as an anticoagulant and centrifuged at 3000 *g*. Plasma was stored at -20°C until required for analysis. Liver function tests (albumin, total protein and alpha-1-acid-glycoprotein (AGP)) were measured also in a baseline serum sample. Any adverse reactions such as changes in arterial pressure or neurological deterioration were recorded during this period. Detailed neurological assessment was not possible because of residual effects of opioids and benzodiazepines and the process of tracheal extubation. Care of the patient was, in all other respects including other drug therapy, as described previously [2].

Bupivacaine concentrations in groups 1 and 2 were compared by Student's *t* test for paired data. The relationship between bupivacaine concentrations and AGP concentrations was determined using linear regression analysis. Values are given as mean (SEM) except where indicated.

Analysis of samples

The assay was performed using HPLC as described by Nation, Peng and Chion [3]. After

the addition of an internal standard (etidocaine), the sample was alkalinized with sodium hydroxide and extracted with dichloromethane. An aliquot of extract was evaporated to dryness at 50°C and redissolved in a mobile phase of 1% triethylamine in water, adjusted to pH 3.0 with phosphoric acid and organic modifier (30% acetonitrile) before injection. The solution was injected onto a $150 \times 4.6\text{-mm}$ column containing $5\text{-}\mu\text{m}$ ultra-sphere "ods" and the flow rate was adjusted to 1.5 ml min^{-1} at ambient conditions. An ultraviolet detector at 205 nm was used. The assay was calibrated with spiked standards. All patients were receiving different medications, including morphine, midazolam, dopamine, prednisolone, azathioprine, cefotaxime, tobramycin, nystatin, ranitidine, folic acid and vitamin K. Control samples of serum from other liver transplant recipients who had not received bupivacaine revealed no interference with the assay. In addition to this study a further 2000 samples have been analysed and no interference from other substances detected [J. Goudie, personal communication]. The sensitivity of the assay was 50 ng ml^{-1} with a within-batch variation of 3.9% and a between-batch variation of 4.0%.

The AGP assay was performed by automated turbidimetric immunoassay using an IL Monarch analyser utilizing "Dako" antiserum to AGP.

Analysis of areas under the concentration-time curves were performed using an "Apple Fitter" programme. The values for $T_{1/2}$ and clearance in

TABLE I. Demographic data and presenting diagnosis of the patients in groups 1 and 2

Patient No.	Age (yr)	Sex	Weight (kg)	Presenting diagnosis
Group 1				
1	17	F	55	Chronic active hepatitis
2	56	F	45	Primary biliary cirrhosis
3	39	M	67	Sclerosing cholangitis
4	58	F	37	Primary biliary cirrhosis
5	29	F	60	Alcoholic cirrhosis
6	45	F	54	Primary biliary cirrhosis
Group 2				
7	26	F	55	Primary biliary cirrhosis (patient studied twice after two separate transplants)
8	52	M	80	Alcoholic cirrhosis + hepatoma
9	40	F	68	Chronic rejection of previous transplant for sclerosing cholangitis
10	59	F	64	Primary biliary cirrhosis + polycystic disease
11	21	F	43	Wilson's disease

TABLE II. Concentrations of plasma proteins and liver function tests in the 11 patients studied. ALT = Alanine transaminase; AGP = alpha-1-acid-glycoprotein; Alk. Phos. = alkaline phosphatase. * 1st transplant; ** 2nd transplant

Patient No.	Albumin (g litre ⁻¹)	Total protein (g litre ⁻¹)	AGP (g litre ⁻¹)	Bilirubin (μmol litre ⁻¹)	ALT (iu litre ⁻¹)	Alk. Phos. (iu litre ⁻¹)
Normal range	30-51	61-77	0.5-1.0	2-17	7-40	30-135
Group 1						
1	46	58	0.9	108	610	43
2	37	67	0.9	150	534	206
3	20	80	0.7	123	78	179
4	35	74	2.3	62	684	783
5	24	55	0.7	14	371	180
6	25	63	2.4	59	456	1200
Group 2						
7	27	51	1.4	867	115	978*
	31	45	1.6	249	674	963**
8	32	53	1.4	368	506	173
9	40	62	1.7	100	969	271
10	38	61	1.1	109	547	200
11	31	45	1.5	18	34	30

this study were not calculated, as sampling was not carried out for the recommended three elimination half-lives because of the need to repeat the injections for analgesia.

RESULTS

The details of the 11 patients studied are shown in table I. The injections were performed at a mean time of 15.7 (SD 8.5) h after the transplanted liver had been reperfused. The concentrations of plasma proteins and liver function tests at the time of each study are shown in table II.

The mean time to complete the bilateral intercostal nerve blocks was 4.5 (SEM 1.8) min.

In group 1 (plain bupivacaine) the mean maximum concentration (C_{max}) was 1.75 (SEM 0.07) $\mu\text{g ml}^{-1}$ (fig. 1). The time at which C_{max} was achieved (T_{max}) was 5, 10 and 15 min in three, two and one patients, respectively. The mean value of C_{max} , in group 2 (bupivacaine + adrenaline), was 1.69 (0.35) $\mu\text{g ml}^{-1}$ after the first injection (fig. 2). T_{max} occurred at 5, 10, 15 and 30 min in one, two, two and one patients, respectively. After the second set of injections in group 2, C_{max} was 1.99 (0.34) $\mu\text{g ml}^{-1}$. T_{max} occurred at 5, 10, 15 and 30 min in two, one, one and two patients, respectively.

C_{max} in group 1 was not significantly different from that after the first set of injections in group 2 ($P > 0.05$), indicating that the use of adrenaline

containing solutions did not reliably slow absorption. The plasma concentrations of bupivacaine had not returned to zero after 6 h in group 2, the time when the second set of injections were performed. In addition, the area under the mean concentration-time curve increased by 44% in group 2 after the second set of injections. These two factors indicate cumulation of bupivacaine. Eight patients had serum concentrations of AGP

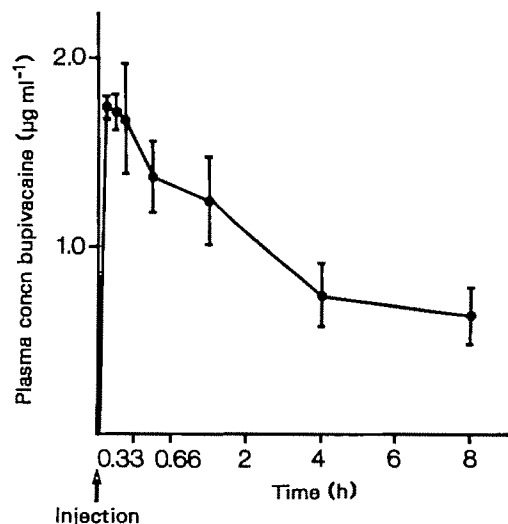


FIG. 1. Plasma concentrations of bupivacaine (mean, SEM) in group 1 after a single set of intercostal injections using bupivacaine 2 mg kg⁻¹.

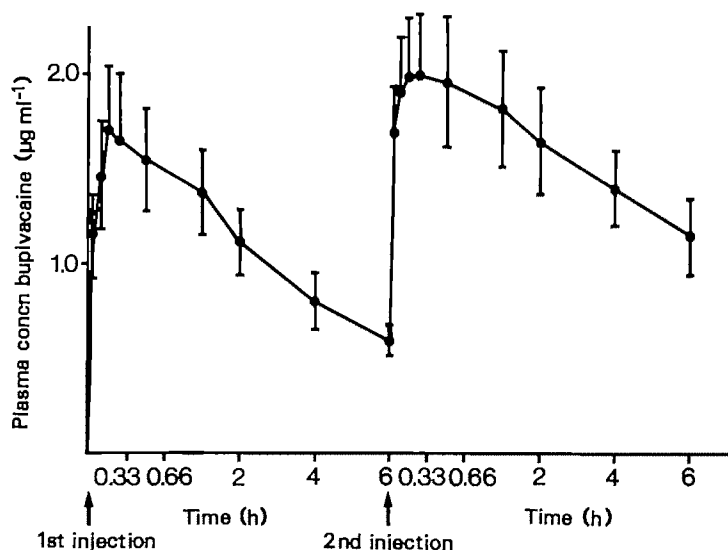


FIG. 2. Plasma concentrations of bupivacaine (mean, SEM) in group 2 after two sets of intercostal injections 6 h apart using bupivacaine 2 mg kg⁻¹ containing adrenaline 1:200 000.

greater than the reference range (table II), but these increased concentrations did not correlate with the measured concentrations of total bupivacaine ($P > 0.05$). The patient who was studied twice had similar plasma concentrations of bupivacaine on each occasion.

DISCUSSION

Intercostal nerve blocks using bupivacaine are an effective method of providing analgesia following liver transplantation and are used routinely at this centre [2]. The technique is chosen in order to limit the dose of opioid. There has been one other short report of intercostal blocks after liver transplantation using bupivacaine in three patients [4]. This study used smaller total doses of 50–100 mg, making comparison of data difficult, but C_{max} occurred at times similar to our data at 5 min, the first sampling time.

Increased plasma concentrations of local anaesthetic may be a problem with intercostal blocks [5, 6] because of the large total volumes of drug solution required for multiple injections in a normally vascular area. In patients with advanced liver disease, the chest wall may have unusually large venous vessels because of porto-systemic anastomoses. These collateral vessels may alter the rate of drug absorption after intercostal injection.

The mean concentrations of bupivacaine were

within ranges similar to those reported in other series [5–7]. There was no statistical difference between C_{max} for the two groups with and without adrenaline. In group 1, the observation that C_{max} occurred at 5 min in two patients not given adrenaline suggests that C_{max} may have occurred earlier in some of these patients. In group II an additional sample was collected at 2.5 min, following reports of C_{max} occurring early [7]. No C_{max} values were seen at 2.5 min in group 2. T_{max} was variable between patients in both groups, but these cannot be compared reliably because of the spacing of sampling times and the relatively small numbers of patients studied. The addition of adrenaline to the bupivacaine solution did not consistently increase the time taken to reach C_{max} and this is in disagreement with other studies measuring arterial concentrations of bupivacaine after intercostal injection [7]. The abnormal vessels of patients with liver disease may not vasoconstrict normally in the presence of injected adrenaline. In addition, the size of the collateral vessels may not be important. Studies in children with extensive collateral vessel formation secondary to coarctation of the aorta have demonstrated that absorption of bupivacaine is the same as that of children with other forms of congenital heart disease without collateral vessel formation [6].

No adverse reactions were seen in these patients, despite plasma concentrations of bupi-

vacaine within the putative toxic range in six patients (two in group 1, four in group 2 following both sets of injections). This may reflect an inaccuracy of the reported toxic threshold of $2-4 \mu\text{g ml}^{-1}$ [8, 9] for bupivacaine. The reported toxic values have been derived from studies using short i.v. infusions of bupivacaine to obtain steady state concentrations. However, differences in the analytical method, sampling sites and infusion regimen used in these studies make interpretation difficult [10]. Alternatively, the lack of adverse side effects may be a reflection of residual benzodiazepine sedation, which had been administered before tracheal extubation [11]. All patients in the study were rousable but had residual sedation and analgesia, making neurological assessment difficult. In addition, the total bupivacaine concentrations measured in our study may not reflect the free, non-protein-bound concentration of the drug which is thought to cause CNS side effects [12].

Bupivacaine is bound extensively to AGP [13], an acute phase reactant with concentrations that were increased in these and other patients following liver transplantation, because of acute surgical stress and liver disease [Shelly, Walker, Burns and Park, unpublished observation]. In the presence of increased concentrations of AGP, increased total concentrations of bupivacaine would be measured, but toxicity might not occur, as the free concentration would be less. The concentrations of AGP were greater than the reference range ($0.5-1.0 \text{ g litre}^{-1}$) in seven of the patients in this study, but did not correspond to those with increased total bupivacaine concentrations. Unfortunately, it was not possible to measure free bupivacaine concentrations or the differing subtypes of AGP [14, 15] and their differing effects (if any) on drug binding. The relatively normal albumin and total protein concentrations reflect aggressive treatment of hypoalbuminaemia by infusion of albumin-containing solutions in the perioperative period.

Other factors also may have contributed to the increased plasma concentrations of bupivacaine. Uptake of bupivacaine by the lungs is significant [16] and may be inhibited competitively by drugs such as propranolol [17]. Three patients had been receiving propranolol for control of portal hypertension before liver transplant. However, these three patients did not develop consistently greater bupivacaine concentrations than the other patients studied. The presence of functional intra-

pulmonary shunting in patients with liver disease [18] may also increase the availability of the drug to the systemic circulation. This has been shown experimentally in animals, using lignocaine [19].

Bupivacaine is metabolized by the liver, with a lesser hepatic extraction ratio than lignocaine [10, 20]. Little is known of drug metabolism shortly after liver transplantation, but studies to date have shown both normal and abnormal pharmacokinetics for several drugs. The transplanted liver is subject to insults during two operations (removal from the donor and insertion into the recipient), with a varying ischaemic time between. Clinical studies have shown that clearance of lignocaine may be impaired in patients with cirrhosis [21], after hepatectomy [22], and during viral hepatitis [23]. No data exist for bupivacaine.

Extrapolation of these results to other patients with liver disease requires caution, as differences in the mechanisms of liver injury may alter its capacity to eliminate bupivacaine. However, the results suggest that caution may be necessary in this group of patients when intercostal blocks are performed. Some patients may achieve potentially toxic plasma concentrations of bupivacaine at a variable time after performing the intercostal nerve blocks. The use of adrenaline-containing solutions did not consistently reduce the speed of absorption or the maximum concentration of bupivacaine. Furthermore, bupivacaine cumulation after repeated intercostal nerve blocks within 6-8 h may occur in some patients following liver transplantation, and possibly others with hepatic dysfunction.

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LOCAL ANALGESIA PREVENTS THE CORTISOL AND GLYCAEMIC RESPONSES TO CATARACT SURGERY

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S. SAPSED-BYRNE AND G. M. HALL

SUMMARY

We studied the metabolic and hormonal responses to cataract surgery in 18 elderly patients, allocated randomly to receive either general anaesthesia or local analgesia by means of a retrobulbar block. Local analgesia prevented the increases in circulating cortisol and glucose concentrations found in those patients who received general anaesthesia. The results show that complete afferent sensory block of the operative site inhibited endocrine and metabolic responses to ophthalmic surgery.

KEY WORDS

Anaesthetic techniques: regional, retrobulbar. Hormones: cortisol. Surgery: ophthalmological, cataract, endocrine and metabolic response.

The effects of different anaesthetic techniques on the endocrine and metabolic response to surgery have been investigated in detail [1]. In particular, the ability of local analgesia to prevent the stress response to pelvic surgery and lower limb surgery has been studied extensively. Engquist and colleagues [2] have shown the necessity for complete afferent neuronal block, both somatic and autonomic, if the pituitary hormonal response to pelvic surgery is to be attenuated.

Ophthalmic surgery, conducted under local analgesia, offers the opportunity of investigating further the effects of total sensory block on the endocrine and metabolic changes associated with surgery. In the present study, we have compared the stress response to cataract surgery in elderly patients, undertaken with either general anaesthesia or local analgesia. Preliminary results have been reported elsewhere [3].

PATIENTS AND METHODS

We studied 18 elderly patients admitted for cataract surgery. They were otherwise healthy and not receiving any therapy known to interfere with the hormonal and metabolic response to surgery. They were allocated randomly to receive either general anaesthesia (GA) or local analgesia (LA). The nature of the study was explained to the patients and informed consent obtained. The study was approved by the Hospital Ethics Committee.

No premedication was given. On arrival of the patient in the anaesthetic room, a central venous cannula was inserted percutaneously via an antecubital fossa vein for collection of blood samples. After a 10-min rest, a control blood sample was collected.

In the GA group, anaesthesia was induced with thiopentone, the trachea was intubated after administration of vecuronium and the lungs were ventilated with 66% nitrous oxide in oxygen supplemented with 0.6–1.0% enflurane. On completion of surgery, residual neuromuscular block was antagonized with glycopyrronium 0.5 mg and neostigmine 2.5 mg. In the LA group, neural block was undertaken with a mixture of equal volumes of 2% lignocaine and 0.75% bupivacaine. Three millilitre was injected as a retrobulbar block and 2 ml placed at the side of the eye to block the facial innervation of the orbicularis muscle.

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In addition to the control blood sample, venous blood was collected after induction of either GA or LA, at the time of nuclear extraction, on completion of surgery, and 30 and 60 min after completion of surgery. The samples were centrifuged immediately and the supernatant stored at -20°C before analysis. Plasma glucose and lactate concentrations were determined enzymatically by methods described previously [4]. Plasma non-esterified fatty acid concentrations were measured by an enzymatic method using acyl-CoA synthetase linked to chromogen production [5]. This method is specific for fatty acids with carbon chain lengths from 6 to 18. Plasma concentration of cortisol was determined by a sensitive and specific radioimmunoassay [6].

The data are presented as mean values (SEM). Statistical analysis was undertaken using one-way analysis of variance, two-way analysis of variance and Fisher's exact test, as appropriate.

RESULTS

There was no significant difference between the groups except for the duration of surgery, which was longer in the LA group (30 min compared with 25 min; $P < 0.05$) (table I). The overall theatre time, however, was similar in both groups (49 min LA group; 47 min GA group).

Plasma cortisol (fig. 1)

In the GA group, cortisol concentrations increased progressively throughout the study from a control value of $348 \text{ nmol litre}^{-1}$ to $747 \text{ nmol litre}^{-1}$ 60 min after completion of surgery. In contrast, in the LA group plasma cortisol concentration did not change during surgery from the control value of $320 \text{ nmol litre}^{-1}$, and then

TABLE I. Details of patients studied (mean values (SEM)).
* Significant difference between mean values ($P < 0.05$)

	LA group (n = 9)	GA group (n = 9)
Age (yr)	73.5 (2.8)	67.9 (5.2)
Weight (kg)	76.1 (2.9)	70.1 (5.4)
Sex	6M:3F	2M:7F
Induction time (min)	13 (2.7)	12 (1.9)
Duration of surgery (min)	30 (2.5)	* 25 (1.4)
Start of induction to leaving theatre (min)	49 (2.9)	47 (2.1)

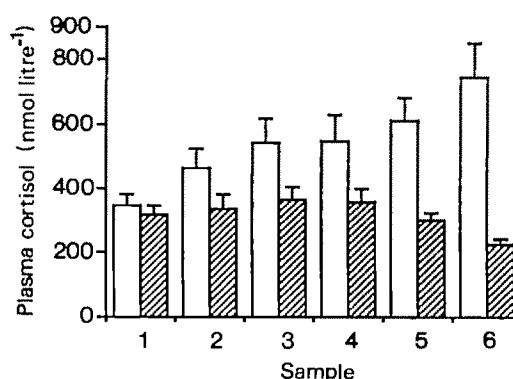


FIG. 1. Mean (SEM) plasma concentration of cortisol in the GA group (open bars) and LA group (hatched bars). Sample 1 = before induction of anaesthesia; 2 = after induction of anaesthesia; 3 = nuclear extraction; 4 = end of surgery; 5–30 min after completion of surgery; 6–60 min after completion of surgery.

decreased slowly to $223 \text{ nmol litre}^{-1}$ 60 min after surgery ($P < 0.05$). There was a significant difference between the groups during surgery ($P < 0.01$) and after surgery ($P < 0.001$).

TABLE II. Mean (SEM) plasma concentrations of glucose, lactate and non-esterified fatty acid (NEFA). * $P < 0.05$ = Significant difference from control; ns = not significant

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	
	Control	After induction	Nuclear extraction	End of surgery	30 min recovery	60 min recovery	GA vs LA
Glucose (mmol litre ⁻¹)							
GA	4.7 (0.2)	4.9 (0.2)	5.1 (0.2)	5.2 (0.3)	5.2 (0.3)	5.1 (0.3)	<i>P</i> < 0.05 Samples 3, 4, 5
LA	4.4 (0.1)	4.5 (0.1)	4.4 (0.2)	4.5 (0.2)	4.5 (0.1)	4.6 (0.2)	
Lactate (mmol litre ⁻¹)							
GA	1.22 (0.08)	1.29 (0.15)	1.29 (0.17)	1.35 (0.15)	1.08 (0.08)	0.99 (0.05)*	<i>P</i> < 0.05 Samples 4, 6
LA	1.33 (0.05)	1.23 (0.05)	1.10 (0.04)*	1.05 (0.05)*	1.02 (0.08)*	0.81 (0.06)*	
NEFA (mmol litre ⁻¹)							
GA	0.91 (0.09)	1.01 (0.12)	1.00 (0.11)	1.12 (0.18)	1.02 (0.16)	1.04 (0.10)	ns
LA	0.90 (0.07)	1.02 (0.10)	1.05 (0.10)	0.95 (0.09)	0.87 (0.09)	0.91 (0.11)	

Circulating metabolites (table II)

Plasma concentration of glucose increased in the GA group from 4.7 to 5.2 mmol litre⁻¹ on completion of surgery, but this change was not significant. In the LA group, plasma concentration of glucose did not alter more than 0.2 mmol litre⁻¹ from the control value of 4.4 mmol litre⁻¹ throughout the study. There was a significant difference in plasma concentration of glucose between the groups at nuclear extraction, at the end of surgery and 30 min after completion of surgery ($P < 0.05$).

In the GA group, plasma concentration of lactate did not alter significantly during surgery from the control value of 1.22 mmol litre⁻¹, but declined significantly to 0.99 mmol litre⁻¹ 60 min after completion of surgery ($P < 0.05$). In contrast, in the LA group plasma concentration of lactate decreased slowly during the study and this resulted in a significant difference between the groups at the end of surgery and 60 min after completion of surgery ($P < 0.05$).

Plasma NEFA concentrations did not change significantly in each group during the study.

DISCUSSION

The results show clearly that cataract surgery under general anaesthesia evokes an endocrine and metabolic response, and that this response can be prevented completely by local analgesia. In the GA group, the plasma cortisol values increased more than two-fold, but the changes in circulating metabolites were relatively small.

The retrobulbar block used to provide LA necessitates the injection of a local analgesic solution around the ciliary ganglion in the apex of the orbit. The ciliary ganglion is a peripheral parasympathetic ganglion of the oculomotor nerve and also contains sympathetic and somatic afferent fibres [7]. The parasympathetic root contains both sensory and motor fibres, the latter supplying the ciliary muscle and sphincter pupillae. The sympathetic fibres arise from the superior cervical ganglion, traverse the ciliary ganglion without synapsing, and supply the dilator pupillae and blood vessels of the eyeball. The somatic afferent component of the ganglion consists of sensory fibres from the eyeball in the short ciliary nerves (ophthalmic branch of the trigeminal nerve). These fibres also traverse the ganglion without synapsing and continue in the nasociliary nerve.

Thus a correctly placed retrobulbar block provides not only somatic afferent, but also autonomic, block of the eyeball. Our results are important confirmatory evidence of the effectiveness of complete deafferentation of the operative site in preventing catabolic hormone secretion during surgery.

The main cause for the glycaemic response to surgery is activation of the sympathoadrenal system [8]. It can be inferred, therefore, that the comparatively small glycaemic response to surgery of 0.5 mmol litre⁻¹ in the GA group reflected only a modest increase in circulating plasma concentrations of catecholamine. This contention is supported by the lack of a significant increase in plasma concentration of lactate in the GA group, as it has been postulated that the lactic acidemia of surgery is an indirect indicator of increased sympathetic activity [9]. Both plasma glucose and lactate concentrations decreased significantly in the LA group, suggesting reduced catecholamine secretion.

The effects of age on the metabolic and endocrine response to surgery have received little attention. Blichert-Toft and colleagues [10] compared the response to inguinal herniorrhaphy in men aged 20–30 yr and 70–75 yr and observed only small differences. Similarly, age was found not to be a significant variable in determining the hormonal and metabolic changes associated with cholecystectomy [11]. We consider it likely, therefore, that the metabolic response to cataract surgery under GA was minor because of the nature of the surgery rather than the age of the patients.

There was no difference between the groups in the total time spent in the operating theatre, although the duration of surgery was longer in the LA group (table I). Thus, perhaps surprisingly, LA offered no advantage over GA in theatre utilization. It was our impression, however, that patients who received LA felt symptomatically better in the immediate postoperative period. This opinion is similar to the observations of Rassan and Thomas [12], who noted the excellent recovery of patients undergoing cataract surgery with LA and patients' preference for this form of anaesthesia.

In conclusion, we have shown that the hormonal and metabolic response to cataract surgery was abolished by LA. Further studies are required to determine if regional analgesia confers any long

term benefit in terms of morbidity and mortality. At present, LA offers metabolic stability in a group of patients who often have severe endocrine and metabolic diseases.

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COMPARISON OF THE RESPIRATORY EFFECTS OF I.V. INFUSIONS OF MORPHINE AND REGIONAL ANALGESIA BY EXTRADURAL BLOCK

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SUMMARY

The incidence of postoperative respiratory apnoea was compared between five patients receiving a continuous i.v. infusion of morphine (mean 73.6 mg) and five patients receiving a continuous extradural infusion of 0.25% bupivacaine (mean 192 mg) in the 24-h period following upper abdominal surgery. Monitoring consisted of airflow detection by a carbon dioxide analyser, chest wall movement detected by pneumatic capsules, and continuous electrocardiograph recorded with a Holter ambulatory monitor. Both obstructive ($P < 0.05$) and central apnoea ($P < 0.05$) occurred more frequently in patients who had a morphine infusion. There was also a higher incidence of tachyarrhythmias ($P < 0.05$) and ventricular ectopic beats ($P < 0.05$) in the morphine infusion group.

KEY WORDS

Analgesia: postoperative, i.v. infusion, extradural. Analgesics: morphine. Complications: apnoea.

Opioid analgesics cause central respiratory depression which is manifest mainly as a reduction in ventilatory frequency and minute volume causing an increase in arterial carbon dioxide tension. Such central depression is usually progressive and predictable, so that intermittent observations are sufficient to detect impending danger to the patient [1, 2]. However, there is increasing evidence to suggest that changes in ventilatory rhythm, and in particular apnoeic episodes, are common in patients receiving opioids for postoperative analgesia [1, 3-7]. These disorders of rhythm are similar to those observed in the sleep apnoea syndrome and are associated

with marked arterial oxygen desaturation [6]. In such patients, sudden death may occur as a result of cardiac arrhythmias induced by hypoxia [3].

This study compared the incidence of central and obstructive apnoeas after upper abdominal surgery in patients receiving an i.v. infusion of morphine or bupivacaine extradural analgesia for pain relief. At the same time, continuous respiratory monitoring using simple equipment was assessed for its value as an apnoea alarm in such patients. Continuous ECG monitoring was carried out to detect any changes in cardiac rhythm.

PATIENTS AND METHODS

Ten patients undergoing elective upper abdominal surgery gave informed consent to participate in the study. They were allocated randomly to receive either a continuous i.v. infusion of morphine or continuous extradural bupivacaine via a thoracic extradural catheter for postoperative pain relief. Premedication comprised oral benzodiazepine (diazepam 5-10 mg or temazepam 10-20 mg). Anaesthesia was induced with thiopentone 4 mg kg⁻¹ followed by a non-depolarizing neuromuscular blocking drug. The trachea was intubated and the lungs ventilated with nitrous oxide and oxygen, supplemented by halothane or enflurane (0.5-1.0 MAC). Up to 200 µg of fentanyl could be given for intraoperative analgesia when considered appropriate by the anaesthetist.

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Patients receiving regional analgesia had an extradural catheter placed at the T7–8 interspace through a 16-gauge Tuohy needle after induction of anaesthesia. Immediately after the operation, they were given an initial dose of 10 ml of 0.25 % bupivacaine through the extradural catheter to produce a block extending between the 6th and 10th thoracic segments. The block was maintained using an infusion of 0.25 % bupivacaine delivered by a syringe pump (Vickers Trionic) at a rate of up to 6 ml h⁻¹, adjusted to maintain a sensory block providing adequate analgesia.

When the patients in the morphine group had recovered consciousness each was given 2-mg aliquots of morphine i.v. at 5-min intervals until comfortable. Analgesia was continued on the ward by means of an i.v. infusion of morphine diluted to 1 mg ml⁻¹ and delivered by a syringe pump (Vickers Trionic) at a rate of up to 4 ml h⁻¹ adjusted to maintain adequate analgesia. All patients were nursed on a High Dependency Unit during the period of the study.

Respiratory monitoring

Respiration was monitored continuously for 24 h. Airflow was detected by two fine-gauge (2-mm external diameter) catheters positioned in the airstream at each nostril, sampling to an infra-red carbon dioxide monitor (Datex). Changes in carbon dioxide concentration corresponded to inspiratory and expiratory air flow. In addition, peak concentrations were recorded.

The patient's chest wall movements were detected by the Cardiff modification [8] of a Graseby apnoea alarm [9]. This consists of three small, pressure-sensitive foam-filled capsules which are taped to the skin, one on each side of the abdomen at the position of maximum excursion and one in the suprasternal notch. Chest or abdominal wall movements cause small volume changes within the capsules. This pneumatic signal is transmitted via a flexible plastic tube which connects each capsule to a sensitive capacitance manometer. The manometer is arranged

as a differential transducer with the suprasternal transducer on one side and the two abdominal transducers on the other. This arrangement effectively increases the sensitivity of the system, because the pneumatic signals from the abdominal sensors are of phase opposite to those from the suprasternal sensor.

The analogue signals from both the carbon dioxide analyser and the apnoea alarm were recorded continuously on a two-channel chart recorder (Chessell). In addition, the signals were relayed to a BBC microcomputer through an analogue-to-digital converter. The computer was programmed to recognize an apnoea and log the time of its occurrence and the duration. The programme recognized central apnoea as an absence of air flow as recorded by the carbon dioxide analyser, together with absence of respiratory movements as recorded by the chest wall monitor, for a period of 10 s or longer. An obstructive apnoea was recognized when there was absence of airflow associated with continued, or exaggerated ventilatory movements, lasting 10 s or longer. The written records of all such episodes were inspected visually to look for evidence of artefacts.

A continuous recording of the ECG was made on a two-channel Holter recorder [10]. This was analysed later for any occurrence of tachycardia > 130 beat min⁻¹, a pause > 1.5 s and any extrasystoles.

The incidence of central and obstructive apnoeas and ECG abnormalities within the two groups were compared by a randomization test for two independent samples [11].

RESULTS

The sex distribution, mean age, weight and height were similar in the two groups (table I). The mean total dose of i.v. morphine administered over the 24-h period was 73.6 mg (range 54–100 mg). The mean total dose of bupivacaine administered

TABLE I. Details of patients studied (mean (range))

	Age (yr)	Sex ratio F:M	Weight (kg)	Height (cm)
Morphine infusion (n = 5)	53.4 (32–66)	4:1	78.2 (50–109)	162 (150–189)
Extradural bupivacaine (n = 5)	53.8 (38–74)	4:1 (53–85)	67.0 (150–178)	161 (150–178)

TABLE II. Respiratory and ECG data. f_R = ventilatory frequency. † Statistical significance of differences between groups

Patient	Mean f_R (b.p.m.)	Mean end-tidal CO ₂ (%)	Obstructive apnoeas	Central apnoeas	Aberrant beats	Tachycardias
Extradural group						
A	22	4.3	0	0	0	0
B	17	5.5	3	1	0	0
C	15	5.2	4	1	2	0
D	18	5.2	0	1	—	—
E	22	4.9	4	0	4	1
Morphine group						
F	22	5.9	9	3	0	0
G	10	7.2	38	3	44	1
H	12	5.7	0	0	—	—
I	15	7.3	4	12	66	26
J	11	6.5	14	11	163	10
P†	< 0.1	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05

extradurally in the same period was 192 mg (range 125–256 mg).

The incidence of both central and obstructive apnoeas was greater in the patients receiving an i.v. infusion of morphine ($P < 0.05$) (table II). The average ventilatory frequency over 24 h was greater in patients receiving regional analgesia, although this was not significant ($P < 0.1$). Two of the patients receiving morphine had episodes of bradypnoea (rate < 8 b.p.m.) lasting more than 5 min. End-tidal carbon dioxide concentrations, averaged for the 24-h period, were greater in the morphine group ($P < 0.01$).

Analysis of the 24-h ECG recordings revealed two technical failures, one in each group. There were no serious life-threatening arrhythmias in either group of patients. However, patients in the morphine group had a greater incidence of aberrant ectopic beats ($P < 0.05$) than in the extradural group. Unfortunately, it was not technically possible to relate these abnormalities to any particular episode of apnoea because the Holter recorder and playback computer could not be time-locked to the respiration monitor recorder. Thus the exact time of occurrence of a particular abnormal complex within the 24-h record could not be determined. Even a small discrepancy between the two records negates any possibility of simultaneous event correlation.

DISCUSSION

Respiratory apnoea may be classified conveniently into two basic types. Central apnoeas are characterized by the absence of respiratory muscle

activity; during obstructive apnoeas there is upper airway obstruction with normal or increased muscle activity [12]. These two distinct types of apnoea can be differentiated by monitoring both airflow and movement of the chest wall.

A sudden change to mouth breathing also may result in failure to detect airflow, but in this case there is a tendency for chest wall movement to decrease rather than increase. Also, such changes last longer than would be compatible with survival if there were total obstruction.

There were obvious differences in the respiratory effects of the two analgesic regimens. The lesser mean ventilatory frequencies and greater end-tidal carbon dioxide concentration observed in the patients receiving morphine reflect its central depressant effect. The episodes of bradypnoea observed in two of the patients are consistent with this and should alert the nursing staff to potential overdose, if noted. The frequent occurrence of apnoea in the patients receiving morphine is more surprising but is similar to that observed previously by Catley and colleagues [1], who found that apnoea, especially when obstructive in nature, was associated with arterial oxygen desaturation. They also found that obstructive apnoea occurred only during sleep.

The detection of a low incidence of apnoea in patients receiving regional analgesia probably reflects both the residual effect of general anaesthesia and asymptomatic periodic respiration during sleep which is a common phenomenon even in the normal population [13]. It is likely that morphine and other opioids increase this tendency in susceptible individuals. Indeed, patients with a

recognized sleep apnoea syndrome display an increased incidence of apnoea during opioid sedation [14].

We have followed others [1] in adopting 10 s of no airflow as the definition of apnoea, which may be too stringent a definition. Indeed, most of the observed apnoeas were of relatively short duration, lasting between 10 and 15 s. However, a few obstructive apnoeas in excess of 20 s were observed and these are more alarming. In the first few days after upper abdominal surgery, patients commonly have reduced arterial oxygen saturation [15–17], thus locating them on the steeper part of the oxygen–haemoglobin dissociation curve and therefore making them more vulnerable to hypoxaemia during disturbances of ventilation [1].

Because of the technical difficulty created by having separate recorders, we were unable to demonstrate a direct causative relationship between a particular episode of apnoea and an arrhythmia. However, as episodes of hypoxaemia can predispose to arrhythmia, the frequent ventilatory disturbances in the patients receiving morphine could account for the group's greater frequency of arrhythmia. The actual number of aberrant beats and episodes of tachycardia are included in table II.

The unpredictability of these apnoeas and their potential danger underlines the useful contribution that reliable, continuous, non-invasive respiratory monitoring would make to patient safety. Our simple, non-invasive equipment was tolerated well by patients, and appeared to detect central apnoeas and obstructive apnoeas unattended for long periods as efficiently as more complex equipment which involves much more intensive management and which is applicable only to selected patients [1]. The use of separate monitors to assess both airflow and ventilatory movement allowed easy differentiation between obstructive and central apnoeas. In addition, the multiple transducers provided a degree of back-up when there was the inevitable displacement of probes. It is difficult to assess the incidence of false positive or negative events in our system, but our overall results are similar to those of other workers [1, 3] using more sophisticated and labour-intensive techniques.

The continuous administration of oxygen to patients in the postoperative period protects them from transient hypoxaemia [6]. However, until reliable routine respiratory monitoring is de-

veloped, the safety of effective infusions of opioids must be in question.

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EFFECT OF I.V. METOCLOPRAMIDE ON GASTRIC EMPTYING AFTER OPIOID PREMEDICATION

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SUMMARY

Metoclopramide was given i.m. or i.v. to patients who had been given an opioid premedication, and the effects on gastric emptying assessed. Forty patients were allocated randomly to one of four treatment groups: group 1, oral diazepam 10 mg; group 2, i.m. morphine 10 mg; group 3, i.m. morphine 10 mg and i.v. metoclopramide 10 mg; group 4, i.m. morphine 10 mg and i.m. metoclopramide 10 mg. Gastric emptying was estimated from the absorption of oral paracetamol. I.v. metoclopramide antagonized the reduction in paracetamol absorption caused by morphine, whereas i.m. metoclopramide did not. This finding may be of importance in anaesthesia for emergencies.

KEY WORDS

Gastrointestinal tract: gastric emptying, metoclopramide. Analgesics: morphine.

The effects of opioids on gastric emptying have been well documented [1]. Gastric emptying is reduced in patients who have been given an opioid premedication [2] and in mothers who have been given opioids for analgesia during labour [3]. The result of delayed gastric emptying is an increased volume of gastric contents at induction of anaesthesia and a subsequent increased risk of regurgitation and aspiration. Metoclopramide is known to increase the rate of gastric emptying [4]. However, two previous studies have shown that i.m. metoclopramide did not antagonize the effects of opioids on gastric emptying [3, 5]. In contrast, there is evidence that i.v. metoclopramide increases the rate of gastric emptying in labouring women who have been given pethidine [6]. There is also evidence that the effectiveness of metoclopramide may depend on the route of administration [7, 8].

The aim of this study was to investigate the effects of i.v. metoclopramide on the rate of gastric emptying in patients who had been given an opioid premedication.

PATIENTS AND METHODS

We studied 40 patients, aged 18-65 yr, undergoing elective surgery. Approval of the local Ethics Committee was obtained, and each patient gave informed consent.

We excluded from the study: patients with diabetes or with known gastric outlet obstruction; those with previous gastric or upper gastrointestinal surgery; patients receiving drugs which affect gastric emptying and those with gastro-oesophageal reflux; possible pregnancy.

Patients were allocated randomly to receive one of four premedications, at least 2 h before surgery.

Group I patients were given diazepam 10 mg orally. Diazepam does not reduce gastric emptying when given orally [9], i.m. [2] or i.v. [10]. This group acted as controls.

Group II patients were given morphine 10 mg i.m.

Group III patients were given morphine 10 mg i.m. and were also given metoclopramide 10 mg i.v., 20 min later.

Group IV patients were given morphine 10 mg i.m. and at the same time, by a separate injection into the lateral aspect of the thigh, metoclopramide 10 mg i.m.

Gastric emptying was assessed indirectly by absorption of oral paracetamol 1.5 g given 20 min after the premedication [11]. As paracetamol is not absorbed from the stomach but is absorbed well from the small intestine, the rate of ab-

sorption of paracetamol may be used as an indirect measurement of gastric emptying. Venous blood samples were taken at 15-min intervals for 90 min, starting immediately before the paracetamol was given. Plasma concentrations of paracetamol were measured using high pressure liquid chromatography [12].

The rate of paracetamol absorption was estimated by: the area under the paracetamol concentration-time curve (AUC) at 45 and 90 min; mean plasma concentration of paracetamol at each time interval; peak paracetamol concentration; time taken to achieve that peak.

Statistical analyses of these data were performed using MANOVA (paracetamol concentrations). Differences between groups were then analysed by Student's *t* test with Bonferroni correction; Student's *t* test (peak concentrations, log AUC); chi-square (patient characteristics data); Kruskal-Wallis test (time to peak).

P less than 5% was taken as significant.

RESULTS

There were no statistical differences between groups in terms of age, sex or body weight (table I). There were no side effects related to the

TABLE I. Demographic data (mean (SD))

	Sex (M/F)	Age (yr)	Weight (kg)
Group I (<i>n</i> = 10)	6/4	35 (7.9)	63 (10.1)
Group II (<i>n</i> = 10)	5/5	36 (16.1)	68 (11.2)
Group III (<i>n</i> = 10)	6/4	39 (12.7)	68 (9.4)
Group IV (<i>n</i> = 10)	8/2	36 (10.9)	73 (11.9)

TABLE II. Mean (SEM) plasma concentrations of paracetamol ($\mu\text{g ml}^{-1}$). **P* < 0.05 compared with group I; †*P* < 0.05 compared with group III

	Time (min)						
	0	15	30	45	60	75	90
Group I	0	11.7	12.6	14.4	15.5	16.4	16.7
	(0)	(4.1)	(3.0)	(3.1)	(2.2)	(1.8)	(2.4)
Group II*†	0	4.4	8.9	7.1	7.7	6.8	6.7
	(0)	(1.9)	(0.8)	(2.4)	(1.9)	(1.6)	(1.3)
Group III	0	17.8	16.6	16.5	15.0	14.0	14.0
	(0)	(4.9)	(2.4)	(2.4)	(2.2)	(1.6)	(1.7)
Group IV*†	0	6.7	7.5	8.9	7.7	7.6	7.2
	(0)	(4.1)	(3.1)	(2.7)	(2.1)	(1.6)	(1.5)

premedication in any of the groups. No patient vomited before operation.

Patients in group I, who received oral diazepam, had significantly greater plasma concentrations of paracetamol than those who received i.m. morphine alone (group II) or those who received both i.m. morphine and i.m. metoclopramide (group IV). The paracetamol concentrations in group III, who received both i.m. morphine and i.v. metoclopramide, were also significantly greater than those in groups II and IV (table II). There were no significant differences in paracetamol concentrations between groups I and III.

The AUC in group I at 90 min was significantly greater than the corresponding AUC in groups II and IV (table III). The AUC at 90 min in group III was also significantly greater than the values in groups II and IV. There were no significant differences between the AUC at 45 min.

The greatest peak concentrations of paracetamol were found in group I (table IV). These did not differ significantly from the peak values in group III, but were significantly greater than the peak values in either group II or group IV. The peak concentrations of paracetamol in group III were significantly greater than those in groups II and IV.

There was a tendency for the time to peak concentration of paracetamol to be shorter in groups I and III; these differences were not statistically significant.

TABLE III. Area under the plasma paracetamol concentration-time curve (SEM) at 45 and 90 min. **P* < 0.05 compared with group I; †*P* < 0.05 compared with group III

	AUC 45 ($\mu\text{g ml}^{-1} \text{ min}$)	AUC 90 ($\mu\text{g ml}^{-1} \text{ min}$)
Group I	471.9 (110.6)	1184.9 (140.5)
Group II	252.7 (90.6)	573.1 (159.6)*†
Group III	639.2 (110.1)	1302.7 (180.4)
Group IV	279.4 (116.4)	630.2 (185.45)*†

TABLE IV. Peak (SD) plasma concentration of paracetamol and time to peak (median and range). **P* < 0.05 compared with group I; †*P* < 0.05 compared with group III

	Peak concn ($\mu\text{g ml}^{-1}$)	Time of peak (min)
Group I	26.09 (8.2)	37.5 (15–90)
Group II	12.23 (11.6)*†	45 (15–90)
Group III	23.89 (12.2)	30 (15–75)
Group IV	13.22 (12.1)*†	45 (15–90)

DISCUSSION

This study has confirmed that premedication with i.m. morphine causes a significant decrease in the absorption of paracetamol compared with premedication with oral diazepam. We have confirmed also Nimmo's original conclusion that i.m. metoclopramide did not prevent a delay in absorption of paracetamol [3]. We have demonstrated, however, that i.v. metoclopramide prevented the delay in paracetamol absorption after opioid premedication. The route of administration of metoclopramide may determine its effectiveness, and Bateman has suggested that the initial peak concentration achieved by an i.v. injection may be necessary to achieve a satisfactory clinical effect [7, 8].

This effect may be important in the patient with a full stomach, treated with opioids before emergency surgery. It should be considered also in the obstetric patient who has received opioids during labour and then requires emergency Caesarean section under general anaesthesia [13]. The effect of metoclopramide on the lower oesophageal sphincter is an additional indication for its use before emergency surgery, when there is a risk of regurgitation and aspiration.

The potential side effects of metoclopramide have been well documented [4]. The incidence of extrapyramidal side effects is approximately 1% when used in low dose [4]. The safety of metoclopramide is confirmed by its use in doses of up to 30 mg kg⁻¹ for patients receiving cytotoxic chemotherapy.

The role of cisapride in anaesthetic practice has recently been reviewed [14]. I.m. cisapride may antagonize the effects of opioids on gastric emptying. However, a parenteral preparation of this drug is not available at present.

In conclusion, we have shown that the effects of opioid premedication on gastric emptying may be antagonized by i.v. metoclopramide. The use of i.v. metoclopramide should be considered in

patients undergoing emergency surgery, even if they have already received an opioid.

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RELATIONSHIP BETWEEN RESONANCE AND GAS EXCHANGE DURING HIGH FREQUENCY JET VENTILATION

E. S. LIN, M. J. JONES, S. D. MOTTRAM, B. E. SMITH AND G. SMITH

SUMMARY

We have studied the relationship between gas exchange and mechanical frequency response during high frequency jet ventilation (HFJV) at 0.5–5.0 Hz in anaesthetized pigs. The mechanical gain curve showed a minimal "anti-resonant" response at 0.8 Hz (f_1) and a maximal "resonant" response at 5.0 Hz (f_2). This finding may be explained by modelling the thorax and abdomen as a system of coupled masses and compliances which undergo two different modes of forced oscillation in the frequency range studied. Gas exchange was optimal in the frequency range between the minimal and maximal responses. The tidal volumes produced were greater than anatomical deadspace, suggesting that gas transport was mainly convective in this range.

KEY WORDS

Ventilation: high frequency, jet. Gas exchange.

Although high frequency jet ventilation (HFJV) has been used for more than a decade, widespread application has been inhibited by a lack of understanding of the mechanisms involved in gas exchange [1]. Consequently, ventilator settings such as frequency, driving pressure and duty cycle (inspiratory:expiratory time, I:E ratio) have been chosen empirically.

Ventilation frequency can influence gas exchange by affecting tidal volume, gas transport mechanisms and gas mixing within the lungs. Gas exchange is dependent also on the mechanical properties of the respiratory system and its frequency response. At resonance, the mechanical response is maximal for a given energy input and

might enhance gas exchange by facilitating bulk gas mixing in the lungs or by increasing tidal volume [2]. The existence of resonance has been demonstrated [3] within the respiratory system during HFJV. Knowledge of the mechanical frequency response of the respiratory system during HFJV may be useful, therefore, in determining which ventilation frequency is associated with optimal gas exchange.

We have investigated the relationship between gas exchange and mechanical frequency response of the respiratory system at ventilation frequencies between 0.5 and 5.0 Hz in anaesthetized pigs. Tidal volumes have been measured in order to study the mechanisms of gas transport.

MATERIALS AND METHODS

We studied 10 healthy Large White pigs of body weight 19–34 kg. Anaesthesia was induced with etorphine (Immobilon) $25 \mu\text{g kg}^{-1}$, and an alphaxalone/alphadolone mixture (Saffan) identical to Althesin 0.05 ml kg^{-1} . After intubation of the trachea with a Mallinkrodt Hi-Lo jet tube, HFJV was applied to the lungs using a prototype Penlon Bromsgrove jet ventilator and an entrainment system (5 litre min^{-1}), both supplying an air in oxygen mixture (Bird Microblender) with an $F_{I_{O_2}}$ of 0.4 (fig. 1). The jet drive pressure

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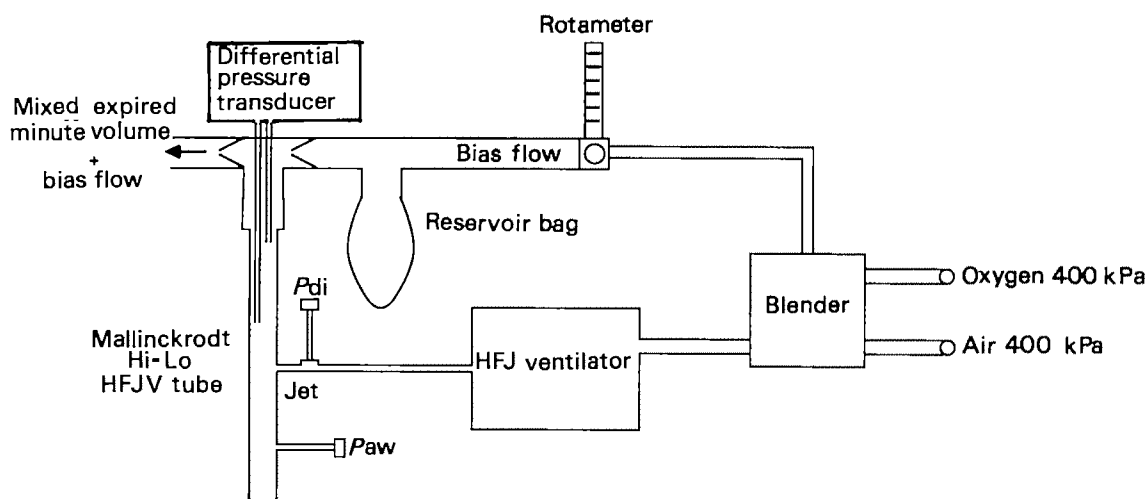


FIG. 1. Schematic diagram of the experimental apparatus.

was maintained constant at 20 lbf in⁻² (approx, 138 kPa) with a duty cycle of 50% (I:E = 1:1).

Anaesthesia was maintained using an infusion of Saffan 0.5 ml kg⁻¹ h⁻¹. Body temperature was kept constant by covering the animal in warm gamgee and using a heated mattress. ECG, intra-arterial pressure and rectal temperature were monitored continuously.

Determination of mechanical frequency response

The mechanical frequency response of the respiratory system was studied by measuring chest and abdominal wall displacement and relating these to the amplitude of the airway pressure signal. Airway pressure was measured using a piezoresistive transducer (Honeywell 162PC01D) calibrated against a water manometer. Displacements of the chest wall at the level of the xiphisternum and abdominal wall at the umbilicus were measured using strain gauges (Lectromed type 4320). Transducer signals were recorded on a multi-channel digital storage oscilloscope (Gould 1604).

Mechanical gain was calculated using the peak-to-trough amplitudes of the strain gauge and airway pressure transducer signals, averaged over eight consecutive breaths, as follows:

$$\frac{|G|}{|S|_{\text{AWP}}} = \frac{|S|_{\text{CSG}} + |S|_{\text{ASG}}}{|S|_{\text{AWP}}}$$

where $|G|$ is the modulus of the gain (i.e. does not contain phase information), $|S|_{\text{CSG}}$ and $|S|_{\text{ASG}}$ are

the chest and abdominal strain gauge signal amplitudes, respectively, and $|S|_{\text{AWP}}$ is the airway pressure transducer signal amplitude. All amplitudes are expressed in volts. $|G|$ is dimensionless because of the use of voltages rather than directly measured units in order to simplify calibration. This approach was used as it was necessary only to detect changes in gain, rather than measure absolute values.

Measurement of gas flow and tidal volume

Gas flow was measured using a differential pressure transducer (Honeywell 162PC01D) connected to a pair of rigid catheters. The catheters were inserted in the tracheal tube via a suction swivel adaptor, with their tips separated by a distance of 5 cm proximal to the jet orifice, so that the lumen of the tracheal tube acted as a pneumotachograph. This was validated for gas flow in both directions, using a bench procedure in which pulses from the jet ventilator were passed through the tracheal tube and catheter mount, collected in a Douglas bag over a known time period, and the gas volume measured using a dry gas meter (S.R.I.). Measured volumes were plotted against the integrated pressure values, confirming the linearity of the system within the flow ranges used (fig. 2).

Entrained and tidal gas volumes were derived by partial integration of the flow curves (fig. 3). As the flow measurement was taken proximally to the jet it did not register injected gas flow during inspiration, but only entrained flow. Flow into the

respiratory system was defined as positive. The volume of gas entrained was represented by the area V_e above the zero line, occurring during inspiration. Area V_{bb} which represented "blow-back" or spill-over volume during inspiration, was calculated as the integrated flow between the negative-sloped crossing of the zero flow line and the end of the jet pulse.

Area V_T , the outward flow during expiration corresponding to expired tidal volume, appeared below the zero flow line during the time when the jet was not active.

Measurement of gas exchange

Arterial blood samples were taken after each change in ventilator frequency (after allowing a

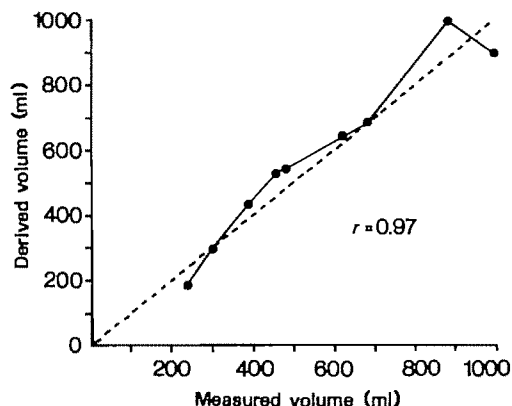


FIG. 2. Graph of derived gas volumes for single breaths at random frequencies in a lung model, obtained by integration of differential pressure trace, plotted against measured gas volumes. The line of identity is shown (—).

15-min period for stabilization) for measurement of gas tensions corrected to body temperature (Radiometer, Copenhagen). Total exhaust minute volume (jet plus bias) was measured in a 1-min period using a Wright's respirometer. Total elimination of carbon dioxide was calculated by measuring the average concentration of carbon dioxide in the expired volume as follows: gas was sampled over a 3-min period into a 1-litre gas syringe, and the concentration determined using an infra-red analyser (P. K. Morgan) calibrated using two known gas standards, accurate to 0.01%. Arterial blood samples were obtained midway through the minute volume measurement for determination of P_{aCO_2} , which enabled a value for the impedance to elimination of carbon dioxide to be determined:

$$\text{CO}_2 \text{ impedance (kPa litre}^{-1} \text{ min)} = \frac{P_{aCO_2} \text{ (kPa)}}{\text{CO}_2 \text{ elimination (litre min}^{-1})}$$

Measurement of chest compliance

Static chest compliance was measured in each animal by inflating the lungs to a given airway pressure and measuring the resulting expired tidal volume using a Wright's respirometer. This was repeated for 15 points over the tidal volume range used experimentally (50–500 ml), the slope of the volume–pressure line obtained by least-squares linear regression being taken as an index of static compliance.

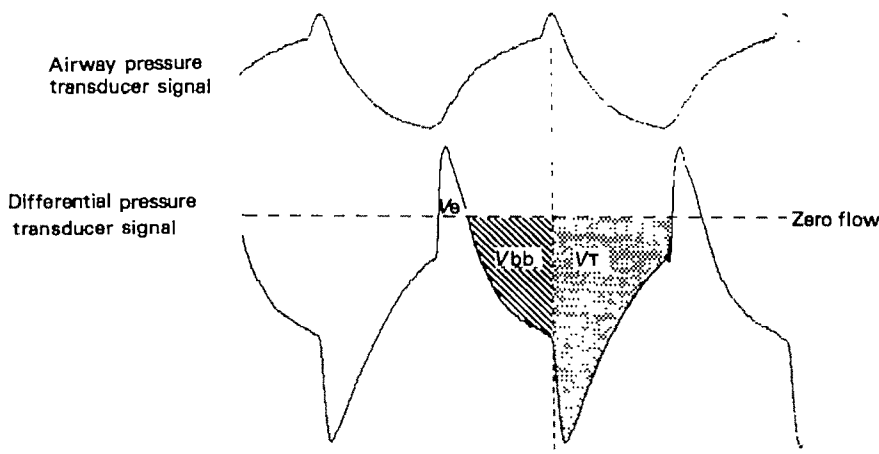


FIG. 3. Airway pressure and differential pressure (flow) transducer signals at 1.5 Hz, drive pressure of 20 lbf in⁻² and I:E ratio of 1:1. Area V_e is the entrained gas volume, V_{bb} the "blow-back" volume during inspiration and V_T the expired tidal volume.

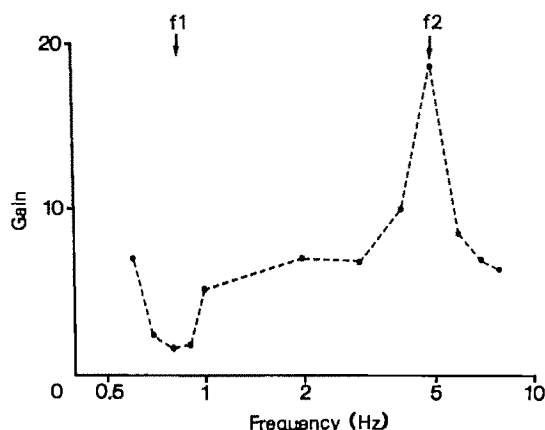


FIG. 4. Mechanical gain-frequency response curve, where $\text{gain} = (S_{\text{CSG}} + S_{\text{AGB}})/S_{\text{AWB}}$. Minimum gain at 0.8 Hz (f_1) and maximum at 5.0 Hz (f_2).

TABLE I. Static respiratory compliance and body weight of the 10 pigs studied

Pig No.	Static respiratory compliance (ml/cm H ₂ O)	Body weight (kg)
1	28.8	19
2	27.5	23
3	46.0	25
4	34.4	25
5	37.1	26
6	26.3	29
7	33.6	29
8	35.3	29
9	42.9	33
10	38.3	34

RESULTS

Mechanical frequency response

Using the airway pressure changes and the chest and abdominal wall displacements, a gain-frequency response curve was plotted for each animal studied (fig. 4). As the animals differed in body weight and compliance (table I), the frequency axis was normalized for these factors. Previous theoretical work [2] has shown that the high gain resonance frequency of the respiratory system may be derived from the formula:

$$f_0 = \frac{1}{2\pi} \sqrt{\frac{S}{LC\rho}}$$

where f_0 = resonant frequency, S = effective cross sectional area of the upper airway, L = effective

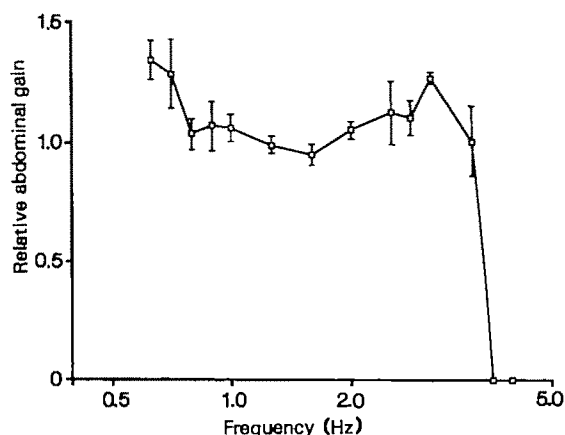


FIG. 5. Abdominal gain response curve (mean, SEM) as a fraction of the mean over-all frequencies. Non-normalized data.

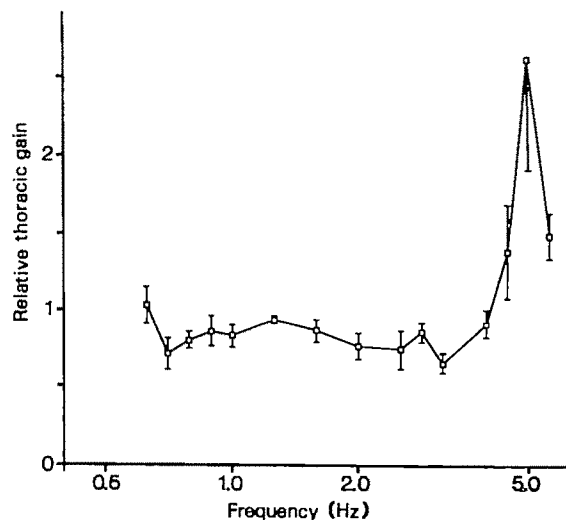


FIG. 6. Thoracic gain response curve (mean, SEM) as a fraction of the mean over-all frequencies. Non-normalized data.

length of the upper airway, C = thoracic compliance, ρ = density of gas.

It has been assumed that S is relatively independent of body weight, whilst L is proportional to body weight (W) and gas density is constant. Thus

$$f_0 = \alpha \sqrt{\frac{1}{WC}}$$

Normalization of each frequency was therefore performed using the following equation:

$$f_n = f_x \cdot \sqrt{\frac{WC}{WC}}$$

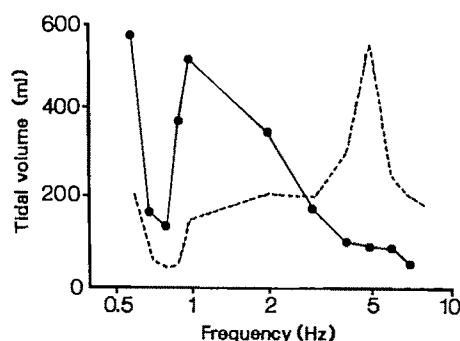


FIG. 7. Tidal volume (—) and gain (---) plotted against normalized ventilation frequency.

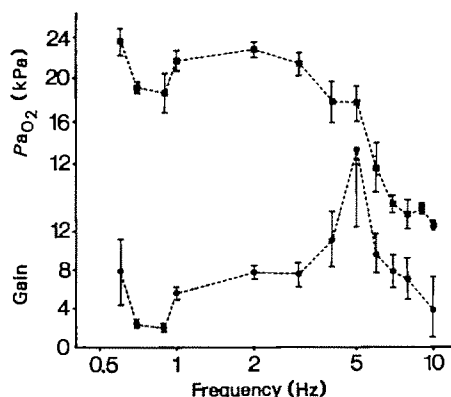


FIG. 8. Variation of P_{aO_2} and gain against normalized ventilation frequency.

where f_n is the normalized frequency, f_x is the measured frequency, $\bar{W}$ is the mean body weight and $\bar{C}$ the mean static compliance of the group. In effect, this equation corrects for the value expected if the animal had average body weight and compliance.

In an adult population it would be expected that S would be proportional to $W^{2/3}$ and L proportional to $W^{1/3}$. However as the animals studied were juveniles, possibly with non-linear growth patterns, this assumption cannot be made. The relationship used was found empirically to produce an acceptable reduction in the scatter of resonant frequencies, and so was used to simplify calculation.

There was a gradual increase in total gain (fig. 4) with ventilation frequency at 1–2.5 Hz, as would be anticipated for a simple resistance-compliance model of the respiratory system.

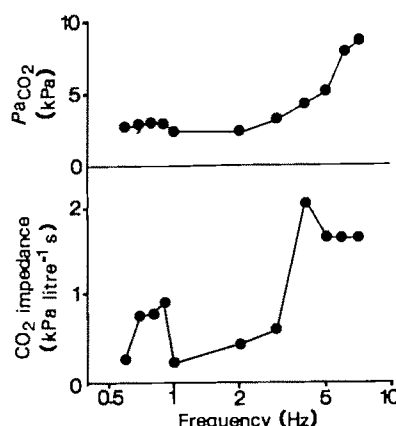


FIG. 9. P_{aCO_2} (top) and carbon dioxide elimination impedance (bottom) vs normalized ventilation frequency.

However, two modes of oscillation were identified which cannot be explained by such a model, with a minimum gain at 0.8 Hz (f1) and a maximal gain at 5 Hz (f2).

Abdominal gain (fig. 5) was obtained by plotting the amplitude ratio of abdominal strain gauge and airway pressure transducer signals against frequency. There was a “cut off” at approximately 4 Hz as abdominal wall movement decreased to undetectable amounts at higher frequencies. There was a sharp peak in thoracic gain (fig. 6) at 5 Hz. Figure 4, showing total gain, is not the sum of figures 5 and 6, as the data in figures 5 and 6 have not been normalized for frequency. This normalization was not applied to the separate abdominal and thoracic data because, although it reduced the population scatter of resonant frequencies, the scatter of “cut off” frequencies was increased, hiding this feature.

Tidal volume

V_T was greater than 300 ml at all frequencies less than 3 Hz, except at f1, where the tidal volume decreased to less than 200 ml (fig. 7). At frequencies greater than 3 Hz, tidal volumes decreased significantly and no change occurred at the maximum gain frequency, f2.

Gas exchange

P_{aO_2} initially decreased at 0.5–0.8 Hz, but recovered at frequencies greater than 1 Hz and remained relatively constant at frequencies up to 3 Hz (fig. 8). The optimal frequency range for oxygenation appeared to lie between the low and high mechanical gain responses. Similarly, the

changes in P_{aCO_2} and derived carbon dioxide impedance plotted against frequency (fig. 9) also appear to be associated with the mechanical gain frequency response, with minimal impedance to elimination of carbon dioxide between the two oscillation modes.

DISCUSSION

Gain-frequency response curve

Thoracic gain (fig. 6) exhibited a maximum (i.e. resonance) at a frequency of 5 Hz (f_2), which is within the range predicted if the thorax behaves as a simple mechanical oscillator with lumped elements defined solely by thoracic properties [1]. This is likely to be the case when the thorax becomes mechanically isolated from the abdomen at frequencies greater than the cut off threshold demonstrated in the abdominal gain curve (fig. 5). At lesser frequencies, the abdomen and thorax interact mechanically as a system of coupled damped resonators, in response to the excitation of the jet pulses. At 0.8 Hz (f_1) the total mechanical gain reached a minimum, lower than predicted for a simple resistance-compliance model; that is, the system exhibited anti-resonance.

The mechanical response of this so-called "coupled oscillation" model may be understood best by reference to electrical analogues, although strict equivalence between components of the electrical model and the anatomical components of the respiratory system cannot be assumed. In this model, inertance is represented as inductance and compliance as capacitance. At the lower frequency (f_1) at which mechanical anti-resonance is occurring, the reactance of the airway gas inertance is negligible, so that the main interaction in the system is between thoracic compliance and the inertance of the abdominal contents. This system behaves as an electrical parallel network and so has a high impedance and low gain as its resonant frequency (gain = 1/impedance within the confines of the definition of gain used in this paper). At higher frequencies, as the reactance of the abdominal inertance increases and the fractional gain of the abdomen is reduced, the interaction is governed almost exclusively by airway inertance and thoracic compliance. These components are analogous to an electrical series circuit with minimal impedance and high mechanical gain at resonant frequency (f_2).

At greater frequencies (> 5 Hz) the thorax may

behave as if isolated mechanically from the abdomen, as the abdominal response appears to be negligible at these frequencies. However, at low frequencies the thorax and abdomen interact to produce an anti-resonant response.

Tidal volume

We found that tidal volume was low where mechanical anti-resonance was occurring (f_1), as would be expected with increasing respiratory system impedance at this frequency. After recovering at frequencies just greater than f_1 , tidal volume decreased as ventilation frequency increased, and no significant change was noted at the resonant frequency f_2 . This may indicate that, at greater frequencies, increased chest and abdominal wall movements resulted in enhanced intrapulmonary gas movement, analogous to the phenomenon of "pendelluft" at lesser frequencies, rather than increasing gas flows in the trachea.

Gas exchange and mechanical response

The frequencies of jet ventilation selected for this study ranged from the upper end of conventional IPPV (0.5 Hz) to 5 Hz; at greater frequencies, gas exchange has been found to deteriorate [4, 5]. Oxygenation was found to deteriorate at f_1 , as may be anticipated from the reduction in tidal volume that occurred at this frequency. There was a corresponding increase in P_{aCO_2} and increase in impedance to elimination of carbon dioxide. Between the oscillation modes f_1 and f_2 , arterial oxygenation and carbon dioxide elimination were maintained well, even though tidal volume decreased. Over this range, tidal volumes approached the expected deadspace volume. As ventilation frequency approached f_2 , tidal volume decreased significantly and both oxygenation and elimination of carbon dioxide deteriorated.

In summary, with frequencies used commonly in clinical practice, and constant jet drive pressure and I:E ratio (1:1), it appeared that gas exchange was maintained within a range of approximately 4 Hz, but a sharp deterioration occurred at the anti-resonant frequency. Over the range of frequencies studied, tidal volumes were generally larger than anatomical deadspace and comparable, at low frequencies, to those used in IPPV. At the high frequency end of the range, tidal volume approached the expected deadspace and gas exchange became less efficient.

We conclude that, during HFJV with these settings and in the given frequency range, gas exchange is dependent mainly on convective transport, rather than the other mechanisms which are involved at greater frequencies and small tidal volumes. At low frequencies, the presence of a mechanical anti-resonance may impair the efficiency of gas exchange during HFJV.

ACKNOWLEDGEMENT

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PREDICTIVE VALUE OF FRC AND RESPIRATORY COMPLIANCE ON PULMONARY GAS EXCHANGE INDUCED BY HIGH FREQUENCY JET VENTILATION IN HUMANS

J. F. PITTET, D. R. MOREL, M. BACHMANN, A. FORSTER
AND P. M. SUTER

SUMMARY

To determine if functional residual capacity (FRC), compliance of the respiratory system (C), or underlying pulmonary disease are predictive for the efficacy of high frequency jet ventilation (HFJV) on pulmonary gas exchange, we investigated six adult patients within 4 h of abdominal surgery and six patients with severe adult respiratory distress syndrome. Gas exchange during intermittent positive pressure ventilation (IPPV) was compared with that during HFJV at frequencies of 100 b.p.m. (HFJV₁₀₀) and 200 b.p.m. (HFJV₂₀₀), resulting in a minute ventilation of about 400 ml kg⁻¹ with both ventilatory frequencies, and in both groups of patients. Baseline FRC and C were measured during IPPV with the multiple-breath nitrogen washout method and from expiratory pressure-volume curves, respectively. Changes in the alveolar-arterial oxygen difference (PA_{O₂} - Pa_{O₂}): Fi_{O₂} ratio induced by HFJV correlated negatively with C (HFJV₁₀₀: $r = -0.78$, $P < 0.005$; HFJV₂₀₀: $r = -0.84$, $P < 0.005$); that is, greater oxygenation was obtained in patients with a better compliance. Similarly, changes in arterial partial pressure of carbon dioxide (Pa_{CO₂}) induced by HFJV correlated negatively with C (HFJV₁₀₀: $r = -0.77$, $P < 0.001$; HFJV₂₀₀: $r = -0.61$, $P < 0.05$). In contrast, there was no significant correlation between FRC measured during IPPV and changes in (PA_{O₂} - Pa_{O₂}): Fi_{O₂} ratio or Pa_{CO₂} induced by HFJV, as these changes were influenced more by the patient's pulmonary disease than by baseline FRC. These results should be interpreted in the context of different

underlying pathophysiological mechanisms reducing FRC in both groups of patients.

KEY WORDS

Lung: functional residual capacity, compliance, gas exchange. Ventilation: high frequency jet ventilation.

Continuous positive pressure ventilation (CPPV) or high frequency jet ventilation (HFJV) improves oxygenation in patients with acute respiratory failure and low pulmonary compliance [1]. Similarly, HFJV has been applied successfully in the postoperative period as an alternative to CPPV to increase functional residual capacity (FRC) and to improve pulmonary gas exchange [2, 3]. However, the relation between the effects of HFJV on gas exchange and pre-existing respiratory mechanics has not been investigated. The aim of the present study was to compare the effects of HFJV on gas exchange in two groups of patients with differing pulmonary impairment, and thus to investigate if FRC and expiratory static compliance (C) measured during conventional ventilation had any predictive value for the efficacy of HFJV.

PATIENTS AND METHODS

Patients

Two groups of patients were studied (table I). The first group comprised six selected patients

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TABLE I. Patient characteristics

Group	Age (yr)	Sex	Height (cm)	Weight (kg)	Surgery, underlying disease
AS	59	M	175	68	Laparotomy for aorto-iliac bypass surgery
	64	M	170	81	
	63	M	175	75	
	56	M	170	68	
	47	M	173	59	
	43	M	163	68	
ARDS	47	F	160	70	Multiple trauma, sepsis
	58	M	174	80	Acute myocardial infarction, sepsis
	31	F	165	60	Acute necrotizing pancreatitis
	46	M	155	60	Acute necrotizing pancreatitis
	52	M	168	91	Mediastinitis, sepsis
	52	M	165	60	Oesophagectomy, sepsis

(age 55 (SD 9) yr, weight 70 (9) kg) who had undergone laparotomy and aorto-iliac bypass surgery (AS). The patients needed short term postoperative ventilatory assistance and were studied within 4 h of the end of surgery. Only patients with lung function in the normal range before operation were included (vital capacity 110 (10.7) % of predicted values in the upright position, FEV₁ 84 (5) %). The second group of six patients (age 47 (5.2) yr, weight 69 (12) kg) were treated in our intensive care unit for severe adult respiratory distress syndrome (ARDS) with a lung injury score of more than 2.5 as defined by Murray [4]. The study was accepted by the committee for ethics in human research of our institution. AS patients gave informed consent to the study before surgery. All patients with ARDS received sedatives and opioids and therefore informed consent was obtained from the patient's closest relative or the referring physician.

Equipment

HFJV was delivered by an MK 800 respirator (Acutronic Medical Systems AG, Jona, Switzerland). Air and oxygen were supplied at a pressure of 4 bar, mixed with a blender and pulsed by an electronically-controlled solenoid valve through non-compliant tubing (120 cm long, 7 mm i.d.). This tubing was connected to a tracheal tube (Hi-Lo-Jet, NCC, Division Mallinckrodt, Inc., Argyle, NY) with three separate lumens: the main lumen was used for IPPV, the first auxiliary lumen (1 mm i.d.) for tracheal pressure monitoring [1], and the second auxiliary lumen (2 mm i.d.) as the "jet insufflation lumen" during HFJV. A bias flow of gas for entrainment was provided by a wide-bore tube connected to

a respirator (CV 2000 Adult Veriflo) delivering 30 litre min⁻¹ of heated and humidified gas at the same inspired oxygen fraction ($F_{I_{O_2}}$) as for jet ventilation. Expiration was through an open T-piece with or without a positive end-expiratory pressure (PEEP) valve. The driving pressure of the ventilator, inspiratory:expiratory time ratio, and ventilatory frequency were adjusted independently and kept constant for each study period.

Intermittent positive pressure ventilation (IPPV) was administered using a volumetric respirator (CV 2000 Adult Veriflo) connected to the main lumen of the Hi-Lo-Jet tracheal tube. In ARDS patients, 10 cm H₂O PEEP was applied throughout the study using an Emerson valve and was maintained during the change of ventilator modes.

Respiratory and haemodynamic measurements

Airway pressure (P_{aw}) was measured with a pressure transducer (Hewlett-Packard (HP) PM 5E+PM 15E) and recorded on a chart recorder (HP 7754 B) via a pressure amplifier (HP 880 5D). Mean P_{aw} was calculated electronically. Ventilatory minute volume ($\dot{V}_E$) and flow were measured using a pneumotachograph (Godart type 17212) with a Fleisch No. 2 head placed in the expiratory limb of the bias flow tubing. Total C was measured from a multiple-step expiratory pressure-volume curve. The curve was recorded on an X-Y recorder (HP 7041 M) following three pulmonary insufflations to obtain a peak P_{aw} of 50–60 cm H₂O. At each 100-ml decrement volume, P_{aw} was allowed to equilibrate for 3 s. C was calculated by dividing the difference in volume corresponding to FRC and FRC+12 ml/kg body weight by the corresponding difference

in P_{aw} on the expiratory limb of the pressure-volume loop.

FRC was measured using a computerized multiple-breath nitrogen washout method [5]. Predicted normal FRC values were taken from the tables of Bates [6] for patients in the upright position. As the patients were in the supine position, 80% of this predicted FRC value was considered normal [6]. As the nitrogen washout method is not appropriate for measuring FRC during HFJV (the high flow delivered by the jet ventilator interferes with the precise measurement of nitrogen concentration), changes in respiratory volume relative to FRC determined with the nitrogen washout method were measured during both types of mechanical ventilation using two bellows pneumographs (Model 108, Pneumograph HP), detecting the change in rib cage and abdominal circumferences, respectively. One pneumograph was fixed around the rib cage at the nipple level, the other around the abdomen at the umbilical level. The bellows were connected to differential pressure transducers (HP PM 131 TC) by a semi-rigid polyethylene catheter (1.3 mm i.d.). The two signals and their sum were recorded on a chart recorder (HP 7754 B) as described previously [7, 8]. Calibration was performed during IPPV by adjustment of the pressure signals to achieve a sum signal (rib cage + abdomen) corresponding to the signal of the pneumotachograph as described by Rouby and colleagues [9]. This method cannot give absolute values of FRC, but only relative FRC changes relative to apnoeic FRC [9]. The following variables were derived from the calibrated pressure signals of the two pneumographs using an on-line data acquisition program of an Apple II microcomputer [7]: ventilatory frequency (f), effective (i.e. injected + entrained gas) tidal volume (V_T = sum of the contributions of the rib cage and the abdomen), $\dot{V}_E$ ($V_T \times f$), rib cage contribution to tidal volume ($V_{T,rc}$), relative changes in end-expiratory position of the sum of rib cage and abdomen excursions, assumed to correspond to changes in FRC.

Mean systemic arterial pressure (SAP) was measured through a radial arterial cannula connected to a transducer (1290 A HP) positioned at the midaxillary line. Cardiac output was measured in duplicate by thermodilution using a 7-French gauge triple lumen Swan-Ganz catheter and Edwards computer (type 9520 A).

Systemic arterial and mixed venous blood

samples were drawn for measurement of P_{aO_2} , P_{vO_2} , P_{aCO_2} and pH with standard electrodes (ABL 330, Radiometer, Copenhagen). Oxygen saturation of haemoglobin was measured with a Co-oximeter (model 182, Instrumentation Laboratories). Alveolar-arterial oxygen partial pressure difference ($P_{A_{O_2}} - P_{a_{O_2}}$) and intrapulmonary venous admixture were calculated with standard formulae.

Procedure

Before the beginning of the study, the patients received morphine 0.1 mg kg⁻¹ and pancuronium 0.1 mg kg⁻¹ i.v. Data were collected during 30 min of HFJV at 100 and 200 b.p.m. applied randomly, separated by 30 min of IPPV. Patients were kept supine during the whole investigation.

FI_{O_2} was maintained constant during the study period (0.4 for AS patients, and 0.5 for ARDS). The effective V_T delivered to the lungs during HFJV was measured using bellows pneumography and set at 4 ml/kg body weight by adjusting the driving pressure at both ventilatory frequencies for each subject group. In a preliminary study, we found that similar ARDS patients required this effective V_T in order to maintain a stable P_{aCO_2} < 6.7 kPa and arterial pH > 7.3.

The following variables were recorded continuously: mean and peak P_{aw} , effective V_T and $\dot{V}_E$, $V_{T,rc}$ and pulmonary volume relative to FRC recorded with the bellows pneumograph system. In addition, SAP and heart rate were monitored continuously. Cardiac output was determined before and at the end of each HFJV period, when arterial and mixed venous blood samples were also collected. FRC and C were determined before and immediately after both periods of HFJV. The reliability of ventilatory volume change determinations with bellows pneumographs was confirmed in six patients (four AS, two ARDS) 60 min after the second period of HFJV, by comparing FRC measured by the nitrogen washout method alone with FRC determined by adding the changes in pulmonary volume recorded by the pneumographs to initial values of FRC (table II). Differences between methods did not exceed 80 ml.

Statistical analysis

The data (mean (SD)) of each group of patients were compared during the five periods of measurements with a one-way analysis of variance

for repeated measurements, followed by a Bonferroni test if the F ratio resulted in a P value < 0.05 . For each period of measurement, both groups of patients were compared using a two-tailed unpaired Student's t test. $P < 0.05$ was considered significant.

RESULTS

Respiratory variables measured during IPPV differed markedly between the two groups of patients (table III, fig. 1). In patients with ARDS, FRC was significantly less than in AS patients (921 (409) ml vs 2106 (539) ml; $P < 0.001$). Mean and peak Paw measured during IPPV were significantly ($P < 0.001$) greater in ARDS than in AS patients, associated with a reduced expiratory

C in ARDS patients (49 (3) ml/cm H_2O), compared with AS patients (108 (25) ml/cm H_2O ; $P < 0.001$). In order to achieve Pa_{CO_2} in the same range in both groups of patients and a clinically acceptable peak $Paw < 45$ cm H_2O , f of IPPV was adjusted to 8–12 b.p.m. in AS patients, and 12–22 b.p.m. in ARDS patients. Similarly, $\dot{V}_E$ in ARDS patients (199 (29) ml $kg^{-1} min^{-1}$) was almost twice that in AS patients (115 (22) ml $kg^{-1} min^{-1}$; $P < 0.001$).

Application of HFJV with the same effective $\dot{V}_E$ of 400 ml kg^{-1} to AS and ARDS patients at both ventilation frequencies induced consistently different responses in gas exchange in the two groups of patients.

In AS patients HFJV produced an immediate and significant two-fold increase in mean Paw (4 (1) to 9 (3) cm H_2O at both frequencies; $P < 0.001$) without change in peak Paw . This was associated with a 25% increase in FRC ($P < 0.001$), a decrease in Pa_{CO_2} ($P < 0.01$) and in $V_{T,rc}$ ($P < 0.002$). These changes in respiratory variables were observed during both HFJV periods. Pa_{O_2} , $(Pa_{O_2} - Pa_{O_2}) : Fi_{O_2}$ ratio, and intrapulmonary venous admixture were unchanged by HFJV (table III, fig. 1). HFJV₁₀₀ and HFJV₃₀₀ did not induce any significant differences in any measured variables other than V_T , including haemodynamic data (table IV). During the second (IPPV₂) and the third (IPPV₃) periods of IPPV, respiratory variables recovered to initial baseline values.

TABLE II. Individual FRC values in six patients at the end of the study, measured with the nitrogen washout technique compared with FRC derived by adding relative changes in pulmonary volume estimated with the pneumograph system to initial measurement FRC, and difference between the two methods

Group	Measured FRC (ml)	Derived FRC (ml)	Difference in FRC (ml)
AS	2320	2400	+80
AS	2647	2647	0
AS	2713	2763	+50
AS	1557	1518	-39
ARDS	500	560	+60
ARDS	1088	1101	+13

TABLE III. Respiratory variables (mean (SD) values of six patients in each group). * $P < 0.05$ between IPPV₁ and HFJV₁₀₀ or IPPV₂ and HFJV₃₀₀; † $P < 0.05$ between AS and ARDS groups

Variable	Group	IPPV ₁	HFJV ₁₀₀	IPPV ₂	HFJV ₃₀₀	IPPV ₃
f (b.p.m.)	AS	8–12	100	8–12	200	8–12
	ARDS	12–22†	100	12–22†	200	12–22†
V_T (ml kg^{-1})	AS	11 (2)	4	11 (2)	2	11 (2)
	ARDS	12 (1)	4	12 (1)	2	12 (2)
$\dot{V}_E$ (ml $kg^{-1} min^{-1}$)	AS	115 (22)	400*	110 (24)	400*	112 (19)
	ARDS	199 (29)†	400*	199 (32)†	400*	195 (30)†
$V_{T,rc}$ (%)	AS	42 (7)	36 (9)*	43 (6)	26 (8)*	43 (6)
	ARDS	43 (14)	39 (19)	45 (16)	43 (19)	45 (15)
Pa_{O_2} (kPa)	AS	12.4 (1.1)	13.1 (3.9)	14.1 (4)	14.1 (3.9)	13.5 (2)
	ARDS	10.7 (3.1)	7.2 (1.5)*†	10.7 (3.1)	6.7 (1.3)*†	12.4 (3.5)
Venous admixture (%)	AS	31 (6)	32 (6)	32 (4)	32 (7)	29 (5)
	ARDS	36 (5)	45 (5)*†	34 (4)	53 (13)*†	32 (5)
Mean Paw (cm H_2O)	AS	4 (1)	9 (3)*	4 (1)	9 (3)*	5 (2)
	ARDS	19 (2)†	13 (4)*†	18 (2)†	12 (3)*	18 (5)†
Peak Paw (cm H_2O)	AS	17 (4)	17 (6)	17 (5)	14 (5)	17 (6)
	ARDS	45 (12)†	25 (6)*†	43 (12)†	20 (4)*†	43 (12)†
FRC (%)	AS	82 (22)	101 (14)*	79 (13)	104 (21)*	74 (12)
	ARDS	37 (16)†	35 (14)†	36 (17)†	37 (19)†	34 (17)†

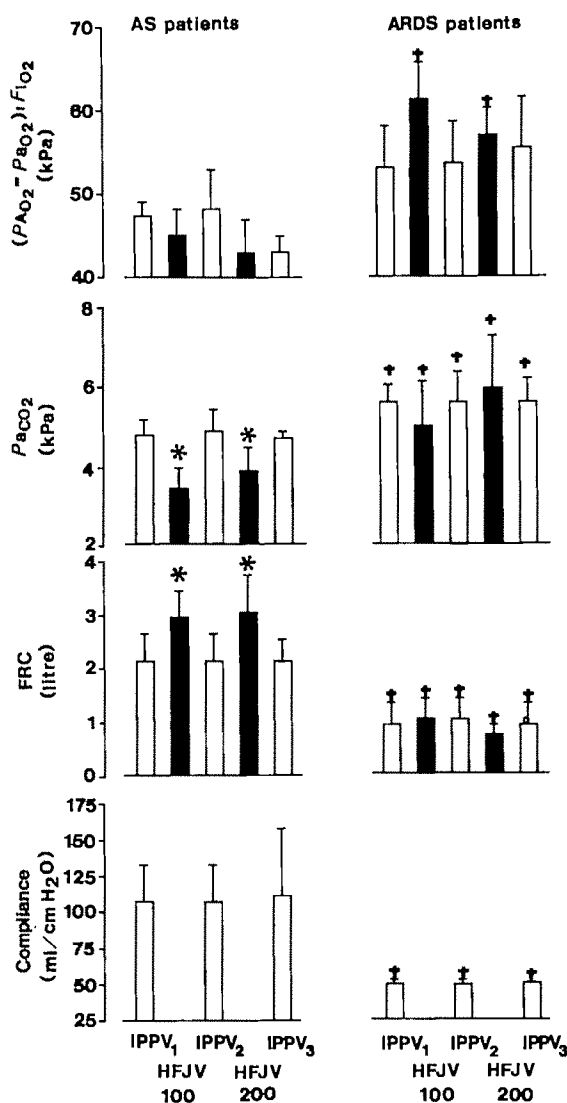


FIG. 1. Mean values (SD) of Pa_{CO_2} , $(PA_{O_2} - Pa_{O_2}) : FI_{O_2}$, FRC and static expiratory compliance in AS and ARDS patients during both types of mechanical ventilation. *Significantly different from IPPV; †significantly different from the same experimental period in AS patients.

Application of HFJV in ARDS patients produced an immediate and significant decrease in both mean and peak Paw , associated with a reduced Pa_{O_2} , an increase in venous admixture ($P < 0.05$), but no change in FRC, Pa_{CO_2} , or $V_{T,rc}$ (table III, fig. 1). As in AS patients, these changes in respiratory variables were observed also throughout both HFJV periods, and respiratory variables recovered to initial baseline values during IPPV₂ and IPPV₃.

To investigate further the different responses in gas exchange in AS and ARDS patients, individual changes in the $(PA_{O_2} - Pa_{O_2}) : FI_{O_2}$ ratio and Pa_{CO_2} with the application of HFJV were plotted against baseline FRC and C values (figs 2, 3). HFJV resulted in $(PA_{O_2} - Pa_{O_2}) : FI_{O_2}$ changes at both frequencies, depending primarily upon

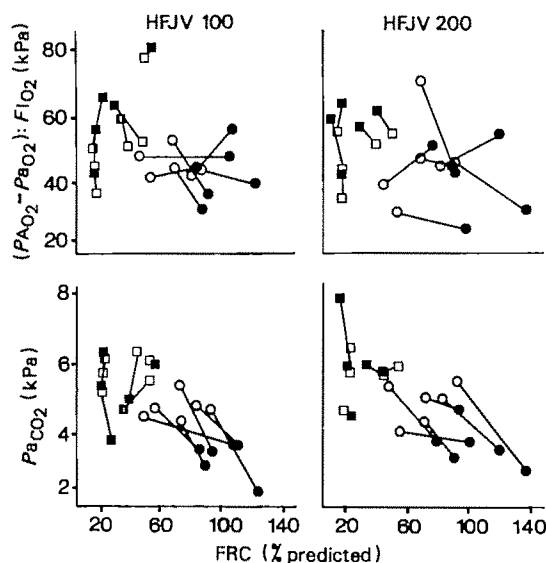


FIG. 2. Individual changes in $(PA_{O_2} - Pa_{O_2}) : FI_{O_2}$ ratio and Pa_{CO_2} from IPPV (open symbols) to HFJV (black symbols) at 100 b.p.m. (left panels) and 200 b.p.m. (right panels) in AS (○—●) and ARDS (□—■) patients in relation to the percentage of their predicted FRC values.

TABLE IV. Haemodynamic variables (mean (SD) values of six patients in each group); No significant differences between IPPV and HFJV at both frequencies of ventilation

Variable	Group	IPPV ₁	HFJV ₁₀₀	IPPV ₂	HFJV ₂₀₀	IPPV ₃
Heart rate (beat min ⁻¹)	AS	97 (21)	105 (18)	102 (19)	108 (19)	102 (26)
	ARDS	121 (19)	122 (16)	121 (12)	119 (15)	124 (11)
SAP (mm Hg)	AS	116 (21)	119 (19)	121 (24)	117 (24)	111 (14)
	ARDS	86 (24)	88 (26)	82 (26)	84 (32)	86 (24)
Cardiac output (litre min ⁻¹)	AS	5.3 (1.4)	4.6 (1.4)	5.6 (1.7)	4.8 (1.5)	5.3 (1.2)
	ARDS	8.3 (2.7)	8.5 (2.4)	9.0 (2.5)	9.4 (3.7)	8.6 (2.7)

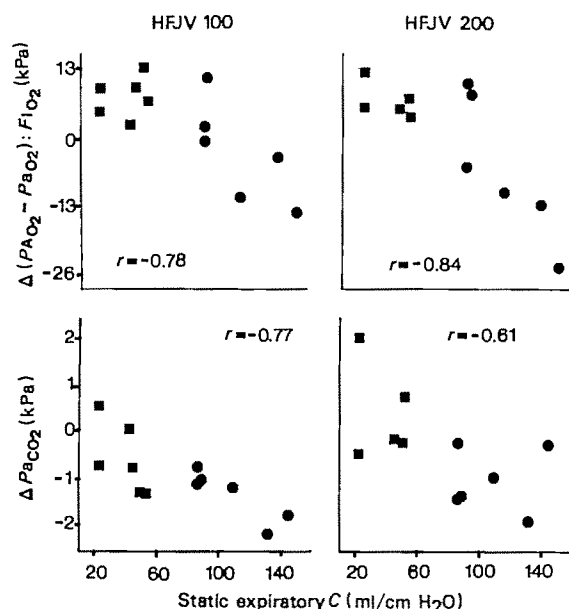


FIG. 3. Individual changes in $(P_{A_{O_2}} - P_{a_{O_2}}):F_{I_{O_2}}$ ratio and $P_{a_{CO_2}}$ induced by HFJV at 100 b.p.m. (left panels) and 200 b.p.m. (right panels) in AS (●) and ARDS (■) patients in relation to expiratory compliance (C).

the patient group rather than upon initial FRC values. In each ARDS patient, HFJV induced a similar increase in $(P_{A_{O_2}} - P_{a_{O_2}}):F_{I_{O_2}}$, irrespective of the baseline FRC, and without changing the latter. In contrast, HFJV increased FRC in AS patients without changing the $(P_{A_{O_2}} - P_{a_{O_2}}):F_{I_{O_2}}$ ratio, even in patients with FRC values similar to those measured in patients with ARDS (fig. 2).

Similarly, pulmonary clearance of carbon dioxide during HFJV was strongly dependent upon the patient group rather than upon initial FRC (fig. 2). Both frequencies of HFJV reduced $P_{a_{CO_2}}$ and increased FRC in every AS patient. In contrast, application of HFJV in ARDS patients did not consistently modify $P_{a_{CO_2}}$ or FRC.

Figure 3 presents individual changes in $(P_{A_{O_2}} - P_{a_{O_2}}):F_{I_{O_2}}$ ratio and $P_{a_{CO_2}}$ induced by HFJV at 100 and 200 b.p.m. in AS and ARDS patients, in relation to expiratory C . In contrast to FRC, there was no overlap of individual C values between both groups of patients. Changes in $(P_{A_{O_2}} - P_{a_{O_2}}):F_{I_{O_2}}$ ratio correlated significantly with C (HFJV₁₀₀: $y = -1.26x + 115.8$, $r = -0.78$, $P < 0.005$; HFJV₂₀₀: $y = -1.72x + 142.5$, $r = -0.84$, $P < 0.005$). Similarly, changes in $P_{a_{CO_2}}$ induced by HFJV also correlated significantly with C (HFJV₁₀₀: $y = -0.014x + 0.061$,

$r = -0.77$, $P < 0.001$; HFJV₂₀₀: $y = -0.016x + 0.867$, $r = -0.61$, $P < 0.05$).

In both groups of patients SAP, heart rate and cardiac output remained stable during the whole investigation (table IV).

DISCUSSION

The results of the present study suggest that FRC measured during IPPV does not predict pulmonary gas exchange during HFJV. In contrast, respiratory compliance assessed during IPPV appears to be an important variable to determine gas exchange during HFJV, as efficacy of HFJV on blood oxygenation and pulmonary elimination of carbon dioxide correlates significantly with respiratory compliance.

Accuracy of the procedure for the calibration of bellows pneumographs has been demonstrated by Rouby and colleagues [9]. In paralysed patients, rib cage and abdomen had the same contribution to V_T ; therefore, their ventilatory system can be considered as an open system having a single independent variable [9]. Consequently, changes in pulmonary volumes can be derived independently from changes in both rib cage or abdominal circumference. These authors used belts connected to differential linear transducers with a frequency response of 60 Hz. The pneumograph system used in our study has a linear frequency response up to 10 Hz [7] that is, three times higher than the highest HFJV frequency used in this study.

We did not measure the contribution of injected, entrained and spilt volumes to V_T . Using thoracic girth transducers, Rouby and colleagues reported that, during HFJV at ventilatory frequencies of 100–600 b.p.m. gas entrainment is at least equal to the injected volume [9]. However, using a new technique which calculates tidal, entrained and spilt volumes by measuring changes in gas flow in the expiration limb of the bias flow tubing of an HFJV circuit, Young recently demonstrated that the entrained volume is only 10% of V_T at both frequencies of ventilation used in the present study [10]. Inspiratory: expiratory time ratio was set at 0.43 for both groups of patients during both HFJV sessions, as suggested as optimal by Rouby [9].

Ventilatory mechanics assessed during IPPV differed markedly in the two groups studied. In AS patients, baseline FRC was only 82 (22)% of the predicted normal value in the supine position,

most probably decreased by the effect of anaesthesia and surgery [11]. Baseline Pa_{O_2} was 12.4 (1.1) kPa with an $F_{I_{O_2}}$ of 0.4, associated with a significant increase in $(Pa_{O_2} - Pa_{O_2}) : F_{I_{O_2}}$ ratio and venous admixture, whereas C and Pa_{CO_2} were in the normal range. As expected, C and FRC of ARDS patients were markedly decreased. In addition, these patients required an almost two-fold greater $\dot{V}_E$ than the AS group to maintain a normal Pa_{CO_2} . Arterial oxygenation of ARDS patients was significantly less, despite a greater $F_{I_{O_2}}$.

In this study we deliberately applied the same effective $\dot{V}_E$ during HFJV to two groups of patients with differing ventilatory mechanics and probably differing carbon dioxide production and oxygen consumption. However, the relation between the efficacy of HFJV on pulmonary clearance of carbon dioxide and effective $\dot{V}_E$ and mean Paw markedly differed in both groups of patients. In the AS group, the increased pulmonary clearance of carbon dioxide during HFJV was related, as during IPPV, to the increment in effective $\dot{V}_E$ and mean Paw . This is in accordance with results of other human studies using HFJV frequencies up to 200 b.p.m. [9, 12, 13]. This relationship suggests that a convective or axial flow transport mechanism, rather than an augmented dispersion, plays a major role in gas transport during HFJV at these frequencies of ventilation [14, 15]. However, dissociation between pulmonary clearance of carbon dioxide and lung volume or mean Paw has been reported with higher frequencies [9], increased expiratory pressure resulting from short expiratory times [16, 17], or increased airway resistance [18]. This dissociation between pulmonary clearance of carbon dioxide and lung volume or mean Paw on alveolar ventilation can be explained by the expansion of the bronchial tree, resulting in an increase in anatomical deadspace [19].

HFJV produced better elimination of carbon dioxide in ARDS patients than in AS patients. Indeed, we did not observe a significant decrease in pulmonary clearance of carbon dioxide during HFJV, despite a decreased mean Paw . These findings are in accordance with the results of Hurst, Branson and DeHaven who did not observe a relationship between improvement in clearance of carbon dioxide and increase in mean Paw during application of HFJV in ARDS patients [20]. Bulk convection alone cannot explain the absence of this relationship. Other gas

transport theories such as the "Pendelluft" effect should be sought, as it may explain the more homogeneous peripheral lung gas concentrations observed during high frequency oscillation than during IPPV in patients with lung regions with significant time constant inequalities [17, 21, 22].

The relation between the efficacy of HFJV on blood oxygenation and mean Paw differed in both groups. The two groups of patients probably had differing distributions of ventilation-perfusion ($\dot{V}_A : \dot{Q}$) ratios. After operation, AS patients with a normal preoperative lung function had a decrease in Pa_{O_2} , associated with an increased $(Pa_{O_2} - Pa_{O_2}) : F_{I_{O_2}}$ ratio, caused possibly by lung regions with low $\dot{V}_A : \dot{Q}$ ratios [23]. ARDS patients may have considerable volumes of lung with $\dot{V}_A : \dot{Q} = 0$, or true shunt [24]. Arterial oxygenation in patients with ARDS depends on alveolar recruitment obtained by using a sufficiently great Paw to open alveoli and prevent them from collapsing during expiration [25]. This may explain why the HFJV-induced decrease in mean Paw in the ARDS group was associated with a worsening in Pa_{O_2} , and venous admixture whereas, in AS patients, no relationship was found between mean Paw and blood oxygenation. Thus the reasons why the effect of HFJV on pulmonary gas exchange is related primarily to the patient's underlying disease and not to FRC are explained by the fact that the pathophysiological mechanisms reducing FRC are different in both groups of patients studied: in ARDS patients, the decreased FRC is caused by loss of endothelial cell integrity associated with non-cardiogenic pulmonary oedema whereas, in patients recovering from major surgery, the reduced FRC is produced by microatelectasis and poorly ventilated lung regions.

In contrast to FRC, expiratory compliance assessed during IPPV correlated well with efficacy of HFJV on pulmonary gas exchange in the groups of patients studied. All ventilatory pressure-volume curves were linear for the segment studied. In particular, no ARDS patients had a compliance curve with an inflection point, as has been described in the early stages of the disease [26]. It has been reported that HFJV has effects similar to those of conventional ventilation on lung morphology, pressure-volume curves and surface tension [27]. It must be concluded that lung stability and compliance are not affected differently during IPPV and HFJV. In the present study, application of HFJV increased alveolar

ventilation more in patients with a better C , resulting in enhanced pulmonary clearance of carbon dioxide. Both frequencies of ventilation produced a similar effect, as demonstrated by similar slopes of the relationship between changes in Pa_{CO_2} and C . As pulmonary clearance of carbon dioxide depends on bulk convection by direct alveolar ventilation with both ventilatory modes used in the present study, in addition to $\dot{V}_E$, clearance of carbon dioxide is mainly a function of C [28]. As previously demonstrated [9, 29, 30], HFJV induces a PEEP effect which depends both on ventilatory settings and on C . At fixed ventilatory settings, the importance of the HFJV-induced PEEP effect is related to the C of the total ventilatory system [9]. In the presence of "stiff" lungs, which tend to decrease the time constant of the total system, the HFJV-induced PEEP effect is less than in patients with normal lungs [9]. Therefore, a greater change in blood oxygenation may be observed in patients with a better C , related to more effective gas distribution and gas mixing [28, 31]. This relationship was observed also in our study, as patients with the best C most decreased their $(PA_{O_2} - Pa_{O_2}) : \dot{V}_{I_{O_2}}$ ratio during HFJV at both ventilatory frequencies.

Application of HFJV decreased significantly the contribution of rib cage to tidal volume at both frequencies of ventilation in AS, but not in ARDS, patients. This decrease in $\dot{V}_{T,rc}$ was inversely related to $\dot{V}_T$ values. We have not found any other study on HFJV which has examined this problem in man. Using inductance plethysmography in rabbits during ventilation by high frequency oscillations, Boynton and colleagues reported that the magnitude of abdominal to rib cage displacements increased with the frequency of oscillations to a maximum near 6 Hz, but thereafter diminished rapidly [32]. Moreover, abdominal relative to rib cage displacements decreased with increasing $\dot{V}_T$ [32]. Similarly, Alleyne, Frantz and Fredberg, studying excised dog lungs ventilated with frequencies similar to those used in our patients, observed that distension of the lung base was favoured [14]. Decrease in $\dot{V}_{T,rc}$ during application of high frequency ventilation in these studies, as in our own, may be explained by the preference for the high velocity inspiratory gas stream to follow relatively straight airway paths [33]. This preferential axial flow to the base of the lungs was not observed in our ARDS patients. This could be related to the distribution of lung lesions in

ARDS, which are typically more severe in dependent regions of both lungs [34].

In conclusion, the comparison of patients investigated after abdominal surgery and patients with severe ARDS suggests that FRC alone measured during IPPV can not predict the changes in gas exchange produced by HFJV. In contrast, the efficacy of HFJV on pulmonary gas exchange depends upon the underlying disease. Arterial oxygenation and clearance of carbon dioxide are improved more (or impaired less) in patients with better compliance. These results have to be interpreted in the context of the different underlying pathophysiological mechanisms reducing FRC in both groups of patients studied.

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A URINARY CYSTEINE-HALOTHANE METABOLITE: VALIDATION AND MEASUREMENT IN CHILDREN

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SUMMARY

An attempt was made in children to identify a urinary halothane-cysteine conjugate which had been described previously in adult patients following administration of halothane. If this conjugate was found it would indicate that a reductive metabolite of halothane binds covalently with the sulphhydryl-containing amino acid, cysteine, a reaction which could lead to hepatic injury. The potential halothane-cysteine conjugate, N-acetyl-S-(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine (acetyl BCFEC), was prepared and the identity of the compound established using hydrogen-1 and carbon-13 NMR spectroscopy and methane chemical ionization mass spectrometry. A measurement technique for acetyl BCFEC was developed using HPLC with u.v. detection at 200 nm. In six children after halothane anaesthesia, one child being studied twice, urine was collected for up to 1 week and analysed for acetyl BCFEC. Little or no acetyl BCFEC was detected in any of the 43 urine samples tested, indicating that in children it is not a significant urinary metabolite of halothane.

KEY WORDS

Anaesthetics volatile: halothane. Biotransformation: fluorometabolites, children, urinary conjugate.

the liver, to form hydrogen fluoride and 2-bromo-2-chloro-1,1-difluoroethylene (BCFE). BCFE is a highly reactive molecule and a potent alkylating agent which could combine with the glutathione components of liver cell organelles, causing hepatic injury and possibly cell death.

Following hepatocyte lysis, the alkylated cysteine form, acetyl BCFEC would appear in the blood and subsequently be excreted in urine. Cohen and colleagues [1] were not able to measure this compound directly but found that, for the first few hours after the i.v. administration of radio-labelled halothane, incorporation of radio-label into a fraction identified as acetyl BCFEC suggested that this was the major urinary metabolite initially, although by 6 h it had disappeared from the urine. If it was established that reductive metabolites of halothane bind to hepatic sulphhydryl amino acids causing cell injury, it would be logical to administer sulphhydryl-containing amino acids during anaesthesia in an attempt to prevent its occurrence. Administration of N-acetyl cysteine is associated with a small risk of life threatening anaphylaxis [2] and should be given only if the benefits outweigh the risks.

BCFE has been reported as an impurity of halothane [4, 5], as a metabolite in man [6] and as a product of chemical decomposition [7]. The possible mutagenicity of BCFE has been studied [8, 9].

The purpose of this investigation was to establish whether or not acetyl BCFEC was a major urinary metabolite of halothane in children.

In a study of eight adult patients in 1975, Cohen and colleagues [1] identified a reductive urinary metabolite of halothane, N-acetyl-S(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine (acetyl BCFEC), following administration of radio-labelled halothane. The authors postulated that halothane was metabolized by cytochrome P450 in

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PATIENTS AND METHODS

2-Bromo-2-chloro-1,1-difluoroethylene (BCFE)

Commercially available material (PCR chemicals, Gainesville, Florida) has been found by Sachdev, Cohen and Simmon [3] to be of only 63% purity. A laboratory synthesis of BCFE developed for the present work is described below. Ice-cold halothane (19.8 g, 0.10 mol) was added to a round-bottom flask containing potassium hydroxide (KOH) (5.6 g, 0.10 mol) pulverized previously in nitrogen. The mixture was refluxed at 90 °C while being stirred vigorously. After 30 min, stirring became difficult because of the formation of a sticky mass. The mixture was cooled in a bath of dry ice in acetone and the liquid which separated was transferred to another flask to which fresh pulverized KOH (5.6 g) was added. Refluxing with stirring was repeated until stirring again became inefficient. Fresh KOH was used as before two more times, and the reaction mixture finally distilled. The fraction boiling at 35–50 °C was analysed on a gas chromatograph (column, 10% carbowax, oven temperature 50 °C, nitrogen flow rate 50 ml min⁻¹, flame ionization detection) and was shown to contain BCFE (retention time 41 s) and halothane (retention time 124 s). Distillation over a short fractionating column increased the height of the BCFE peak compared with the halothane peak. Carbon-13 NMR data of halothane and of BCFE are given in table I.

Synthesis of acetyl BCFEC

To 2 ml of a solution of N-acetyl-L-cysteine (0.326 g, 2.0 mol) in 1:1 v/v aqueous methanol was added 4 ml of sodium hydroxide 1 mol litre⁻¹ in the same solvent at an ice-bath temperature. After 15 min, BCFE 3 mmol, in admixture with halothane at -70 °C, was added. Stirring at an ice-bath temperature was continued for 30 min. The mixture was allowed to reach room temperature while stirring was continued for 150 min.

The product mixture was cooled and acidified to pH 3–4 with 4 ml of hydrochloric acid 1 mol litre⁻¹ until precipitation occurred. The white solid collected by filtration was dissolved in ethyl acetate 30 ml. The filtrate was concentrated at room temperature under reduced pressure and extracted with ethyl acetate 40 ml. The combined ethyl acetate solutions were washed three times with 10 ml of water each and dried over anhydrous sodium sulphate. On evaporation of ethyl acetate, 150 mg of acetyl BCFEC, melting point 136–138 °C, was obtained. On crystallization from a mixture of ethyl acetate and hexane, needle-shaped crystals were obtained with a melting point of 141–143 °C. The above procedure is a modification of that of Sachdev and colleagues [manuscript in preparation].

Patient details

These are described in detail in the accompanying paper [10] and are only summarized here. Patients Nos 1–5 were healthy children having elective surgery. Patient six had cystic fibrosis, chronic lung disease and proven liver disease; he had a choledochoduodenostomy to bypass a stricture at the lower end of the common bile duct. Halothane 1% v/v was administered from a Mark III Fluotec vaporizer for 1 h and patient uptake determined. Urine was collected continuously for up to 1 week and analysed for acetyl BCFEC.

Identification of acetyl BCFEC

Acetyl BCFEC from the above-described synthesis was subjected to analysis by hydrogen-1 and carbon-13 nuclear magnetic resonance (NMR) spectroscopy, with d⁶-dimethylsulphoxide as solvent (table II), and methane chemical ionization mass spectrometry (table III). All spectral data were consistent with the titled structure.

Measurement of acetyl BCFEC

Acetyl BCFEC was measured by high pressure liquid chromatography (HPLC), a Waters 480

TABLE I. Proton-decoupled carbon-13 NMR spectra of halothane and BCFE in CDCl₃ with chemical shifts δ relative to CDCl₃ ($\delta = 77.0$)

Halothane			BCFE		
Carbon	δ (p.p.m.)	$J_{C,F}$ (Hz)	Carbon	δ (p.p.m.)	$J_{C,F}$ (Hz)
—CHBrCl	50.1 q	41	= CBrCl	72.0 dd	40, 47
—CF ₂	121.1 q	278	= CF ₂	154.2 dd	287, 292

TABLE II. Hydrogen-1 NMR and proton-decoupled carbon-13 NMR spectra of acetyl BCFEC in CD_3SOCD_3 , with chemical shift δ relative to $Si(CH_3)_4$ ($\delta = 0$) and to CD_3SOCD_3 ($\delta = 39.6$), respectively

δ (p.p.m.) of hydrogen-1	$J_{H,H}$ (Hz) or $J_{H,F}$ (Hz)	Assignment	δ (p.p.m.) of carbon-13	$J_{C,F}$ (Hz)
1.87		CH_3	22.4	
3.24 m		$\beta-CH_2$	30.1 t	3
4.45 dt	5,5, 8.2	$\alpha-CH$	52.1	
7.03 dd	8,6, 9.4	$CHClBr$	57.5 t	33
		CF_2	126.9 t	285
8.4 d	8.2	NH		
		CO	169.6	
		COOH	171.4	

TABLE III. Methane chemical ionization mass spectra of acetyl BCFEC and its methyl ester

Acetyl BCFEC			Methyl ester	
m/z	Relative abundance (%)	Assignment	m/z	Relative abundance (%)
344, 342, 340	15, 59, 40	MH^+	358, 356, 354	5, 20, 16
324, 322, 320	5, 15, 8	$MH-HF$	338, 336, 334	2, 6, 5
304, 302, 300	4, 8, 6	$MH-2HF$	318, 316, 314	0.5, 1, 1
302, 300, 298	8, 21, 15	$MH-CH_2CO$	316, 314, 312	1, 7, 6
262, 260, 258	9, 23, 17	$MH-CH_2CO-2HF$	276, 274, 272	10, 33, 24
162	100	$CH_3CONHCH(COOR)CH_2S$	176	100
130	58	$CH_3CONHCH(COOR)CH_2$	144	65

ultraviolet detector at 200 nm, Waters M 6000 pump and a Rheodyne 7125 sample injector. The column was a 25-cm, 4.3-mm Serva, 5- μ m RP-18 Spheri-5 column. The mobile phase consisted of sodium phosphate 40 mmol litre⁻¹ pH 4.0, 14% (v/v) methanol, 14% (v/v) acetonitrile and 0.16% tetrabutylammonium hydroxide (TBAH) (Aldrich, Milwaukee, Wisconsin) in water. Using synthesized acetyl BCFEC, a single peak was obtained on HPLC. The identity of the 200-nm HPLC peak as acetyl BCFEC was confirmed by repeatedly injecting 50- μ l samples of a 5-mg ml⁻¹ aqueous solution and collecting mobile phase fractions from the detector outlet as the peak appeared. The combined fractions were evaporated by rotary evaporation at reduced pressure and analysed by hydrogen-1 NMR spectroscopy. The spectrum of the compound being measured was identical with that found for synthesized acetyl BCFEC. Measurement of acetyl BCFEC was linear from 0.7 to 1000 μ mol litre⁻¹ (CV for eight replicates of a 50- μ mol litre⁻¹

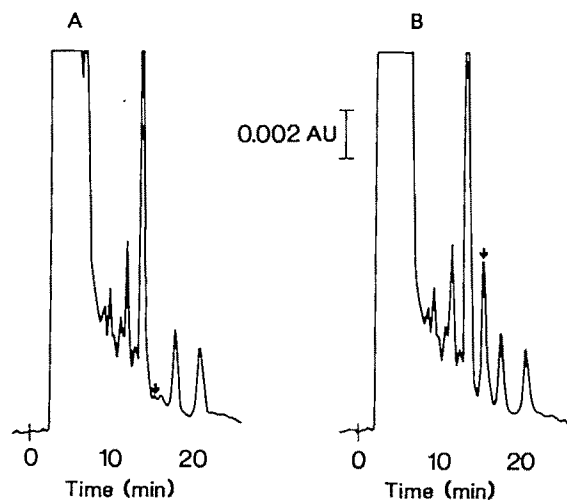


FIG. 1. HPLC measurement of urinary N-acetyl-S(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine (acetyl BCFEC). A: Sample taken from a patient's first 24-h collection after halothane anaesthesia. B: The same sample spiked with acetyl BCFEC 50 μ mol litre⁻¹.

TABLE IV. Details of urinary excretion of TFA and acetyl BCFEC after halothane anaesthesia in children. No acetyl BCFEC was detected in any of the 43 urines tested. †This ratio was calculated on the assumption that acetyl BCFEC was excreted at just below the detectable limit, an unlikely possibility

Patient No.	Duration of post-op. urine collection (days)	TFA		Excretion of acetyl BCFE below those shown would not have been detected (μmol)	†Ratio of TFA: acetyl BCFEC
		Total excretion (mmol litre^{-1})	Absorbed halothane excreted as TFA (%)		
1	3	0.84	6.28	1.14	740
2	8	2.92	12.34	3.42	854
3	7	2.04	11.72	2.38	857
4	4	4.62	18.20	2.51	1839
5	7	4.65	12.45	2.91	1598
5	7	4.55	9.25	3.40	1338
6	7	4.33	9.56	8.02	540
Mean (SD)			11.4 (3.4)		

standard was 1.5%). The lower limit of detection was $0.7 \mu\text{mol litre}^{-1}$. Separation of acetyl BCFEC from other u.v. absorbing constituents of urine was confirmed by comparing the chromatograms of unspiked urine and urine spiked with acetyl BCFEC $50 \mu\text{mol litre}^{-1}$ (fig. 1).

RESULTS

In the six patients studied all 24-h urine samples were analysed for trifluoroacetic acid (TFA) and acetyl BCFEC (table IV). A very small peak of u.v. absorbing material with retention time identical to that of acetyl BCFEC was found in some of the urine samples. This peak was found sometimes in control urine samples taken before anaesthesia and in the urine samples collected soon after anaesthesia. This suggested that even the small amount of u.v.-absorbing material detected in urine at the retention time for acetyl BCFEC probably included other compounds in addition to acetyl BCFEC. However, by making the assumption that this material detected was entirely acetyl BCFEC, we could determine an upper limit for the excretion of acetyl BCFEC in children. The upper limit for the acetyl BCFEC:TFA ratio varied from 1:540 to 1:1840.

DISCUSSION

Studies in animals [11–15] using radio-labelled halothane have demonstrated binding of halothane metabolites to liver cell proteins and phospholipids. This has been interpreted

as evidence to explain the cause of hepatic dysfunction in some patients after halothane anaesthesia. In these studies, covalent binding of halothane metabolites to hepatocytes was not correlated with clinical, biochemical or histological evidence of hepatic dysfunction. Experimental evidence with paracetamol suggests that covalent binding of metabolites to hepatocyte macromolecules is in itself insufficient to explain paracetamol-induced cellular toxicity [16, 17].

It has been postulated that, under reductive (hypoxic) conditions, hydrogen fluoride is eliminated from halothane by cytochrome P450 [11, 12], with the formation of 2-bromo-2-chloro-1,1-difluoroethylene (BCFE), a reactive molecule and a potent alkylating agent. Cohen and colleagues [1] injected eight adult patients with ^{14}C -labelled halothane and identified three major urinary metabolites: N-trifluoroacetyl-2-aminoethanol, TFA and acetyl BCFEC. The finding of acetyl BCFEC in the urine of these eight patients following halothane was taken as evidence to support the reductive theory. These authors speculated that BCFEC reacted with intrahepatic amino acids, particularly glutathione and cysteine, causing cell death, and that, as dead hepatocytes underwent enzymatic degradation, glutathione and cysteine derivatives of BCFEC were released into the blood and subsequently excreted via the kidney.

In the six children studied in our investigation acetyl BCFEC, if present at all, occurred in only trace quantities. The maximum percentage of absorbed halothane which potentially could have

been metabolized to acetyl BCFEC was 0.11%. Thus in children, acetyl BCFEC is not a major urinary metabolite of halothane. The urinary pharmacokinetics of acetyl BCFEC described by Cohen and colleagues [1], with maximum excretion in the first 1 h after anaesthesia, is inconsistent with a drug metabolite which involves covalent binding to hepatocytes, but suggestive of an artefact of the radio-label experiment or an impurity.

A more typical urinary excretion pattern was found in the study by Cohen and colleagues [1] for TFA excretion, a known metabolite of halothane [18–20]. TFA did not appear in the urine until the second hour and took 6 h to reach peak excretion. Our inability to find substantial amounts of acetyl BCFEC and the unusual time course of excretion described by Cohen and colleagues [1] lead us to doubt if the substance measured by this group was a genuine metabolite of halothane.

In children, following halothane anaesthesia, we have been unable to demonstrate a significant quantity of a halothane–cysteine conjugate which would confirm a role for cysteine in halothane detoxification. We do not recommend that the sulphur-containing amino acids or derivatives methionine, cysteine, N-acetylcysteine or glutathione be administered to children during halothane anaesthesia in an attempt to reduce the potential for hepatotoxicity.

ACKNOWLEDGEMENT

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HALOTHANE METABOLISM IN CHILDREN

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SUMMARY

Halothane (1% v/v inspired) was administered for 60 min to six children of mean age 74 months (range 14-119 months). Uptake of halothane was measured from the difference in the concentration in inspired and expired gas and varied from 176 to 310 mg kg⁻¹, depending on minute ventilation. After administration of halothane ceased, its elimination in expired gas was measured in four patients until the conclusion of anaesthesia; 32-37% of the absorbed halothane was expired 90 min after halothane administration ceased. Urinary excretion of trifluoroacetic acid, fluoride and bromide was measured for up to 1 week. Of the absorbed halothane, 11.4% (range 6.3-18.2%) was excreted in urine as trifluoroacetic acid and 0.37% (range 0.10-0.64%) as inorganic fluoride. The urinary half-life of trifluoroacetic acid was 41.8 h (range 10.4-59.1 h). The quantitative and qualitative metabolism of halothane via the reductive and oxidative pathways in children are comparable to values found in adults. No differences in the metabolism of halothane by children were found which would explain the different incidence of halothane-associated hepatitis compared with adults.

KEY WORDS

Anaesthetics volatile: halothane. Biotransformation: halothane. Anaesthesia: paediatric.

Halothane is the volatile anaesthetic agent used most commonly in children. On rare occasions, fulminant postoperative liver failure follows its use [1]. The incidence of liver failure following halothane in children is lower than in adults [2]. Why this difference exists is unknown. One suggested explanation is that halothane is metabolized less in children than in adults, and that metabolism proceeds via different metabolic pathways and at different rates [3]. This study was

performed to quantify halothane metabolism in children.

PATIENTS AND METHODS

The hospital Ethics Committee approved the investigation and informed parental consent was obtained for each patient. Five children were studied once and one child was studied twice, with an interval of 9 months. Five were healthy children (table I), but patient No. 6 (a 119-month-old boy of 35.8 kg) had cystic fibrosis.

Biopsy showed moderate patchy fatty change in the liver and the preoperative arterial haemoglobin saturation was 91% ($F_{I_{O_2}}$ 0.2). Blood was taken for liver function tests the day before surgery and on the fourth day after operation to assess the effect of halothane and biliary surgery on liver function. Additional postoperative blood samples were not taken to measure liver enzymes, as it was considered this would cause unnecessary distress in an emotional patient. Liver function tests were performed in this child as it was possible that arterial hypoxaemia, moderate fatty liver disease and surgery on the biliary system might have affected halothane metabolism, hepatocyte viability, or both.

Anaesthetic technique and gas sampling methods

Patients were premedicated 1 h before surgery with i.m. papaveretum 300 µg kg⁻¹ and hyoscine 6 µg kg⁻¹. Anaesthesia was induced and maintained with oxygen 2 litre min⁻¹ and nitrous oxide 4 litre min⁻¹ administered via the one-way valve system shown in figure 1.

Muscle paralysis was achieved with alcuronium 300 µg kg⁻¹ and the trachea intubated with a snug fitting plain tracheal tube which allowed no leak at a pressure of 15 cm H₂O. The lungs were

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TABLE 1. Patient details. * Bilateral hip surgery for Perthe's disease. † Cystic fibrosis with stenosis of the distal end of the common bile duct. Liver biopsy showed moderate fatty change. His medications were ticarcillin, tobramycin, vitamin E, pancrease and multivitamins

Patient No.	Age at operation (months)	Weight (kg)	Surgical procedure	Duration of anaesthesia (min)
1	14	9.7	Hypospadias repair	90
2	39	15.0	Pelvic/femoral osteotomy	200
3	47	14.5	Pelvic/femoral osteotomy	190
4	88	28.5	Pelvic/femoral osteotomy	115
5	101	32.5	Pelvic/femoral osteotomy	190
5*	110	35.7	Pelvic/femoral osteotomy	225
6†	119	35.8	Choledochoduodenostomy	300
Mean (SD)	74 (37)	24.5 (10.3)		187 (64)

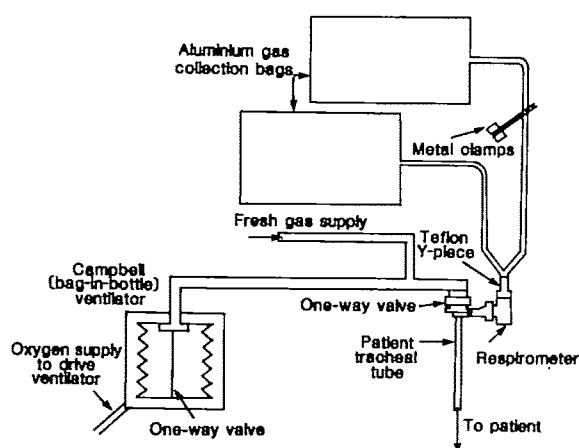


FIG. 1. Anaesthetic circuit.

ventilated with a Campbell time-cycled, pressure-limited ventilator (Ulco Engineering, Sydney, Australia). An in-line halothane analyser and an end-tidal carbon dioxide monitor were not available for use. Visually adequate ventilation was achieved by adjusting inspiratory pressure and rate of ventilation. The adequacy of ventilation was checked by auscultation with a precordial stethoscope, the systolic arterial pressure measured manually with a sphygmomanometer and the ECG monitored. After 10 min stable ventilation, 1% v/v halothane was added to the inspired gas mixture for 60 min. Halothane was administered via a Mark III Fluotec vaporizer which had been calibrated recently with a refractometer; the 95% confidence limits of the 1% v/v dial setting were 0.85–1.1%. Inspired gas samples from the fresh gas line were collected every 15 min into gas-tight glass syringes (SGE, Ringwood, Victoria, Australia) and the halothane concentration measured by gas chromatography.

Expiratory minute ventilation was measured with a Wright's respirometer (C.I.G. Medishield) which had been calibrated recently against a counterbalanced waterseal spirometer. The accuracy of measuring gas volumes greater than 5 litre was $\pm 2\%$. The total expired gas from each patient was collected continuously into 30-litre aluminium foil gas-tight bags (Smorgon Pty Ltd, Rosebery, Sydney, Australia). A new bag was used every 4 or 5 min, depending on the patient's minute ventilation. Anaesthesia proceeded uneventfully in all patients and hypotension, hypoxia and hypovolaemia were not observed either during or after operation. No patient required a blood transfusion and estimated blood loss in all patients was less than 10% of the calculated blood volume. At the conclusion of surgery, neostigmine $50 \mu\text{g kg}^{-1}$ and atropine $20 \mu\text{g kg}^{-1}$ were given. The trachea was extubated when the patient was awake and regular spontaneous ventilation established.

Residual halothane in expired gas was measured by gas chromatography. Contamination of exhaled gas by the inspired gas mixture was avoided using a one-way valve in the non-rebreathing circuit. No flow was recorded by the respirometer in inspiration, confirming the competence of the one-way valve. In four patients, expired breath collection was continued after administration of halothane stopped. Because of difficulties in getting young children to co-operate, breath collections were discontinued after tracheal extubation and thus the total amount of halothane eliminated in the expired breath could not be determined. Halothane uptake was calculated from the patient's inspiratory and expiratory halothane concentration and minute ventilation. Halothane absorbed by the rubber of the fresh gas line, the plastic of the one-way valve and the

tracheal tube was not determined. This resulted in over-estimation of halothane absorption by the patient of less than 1% of the total uptake [4, 5]. Halothane concentration measurements were made within 5 h of sampling. The aluminium foil collection bags were found to lose only 2% of the initial halothane content after storage for 16 h.

Measurement of halothane urinary metabolites

A fluid balance chart was kept for all patients during their hospital stay. The volume of oral and i.v. fluids was measured. All urine was collected daily and stored at -10°C until analysis for fluoride (F^{-}), bromide (Br^{-}), trifluoroacetic acid (TFA), chloride (Cl^{-}) and creatinine (Cr). The daily excretion of halothane metabolites and the daily excretion of Cl^{-} and Cr were calculated from urine volume and metabolite concentration. Twenty-four hour urine collections were complete on 39 occasions and incomplete on four. In one 14-month-old boy who had a repair of hypospadias, there was a small leakage of urine around a urinary catheter. Because of a nursing error, a 10-h urine collection from an 88-month-old boy was discarded after its volume was measured. One 47-month-old girl wet the bed on four occasions and the estimate of two 24-h urine volumes was unreliable. Daily creatinine excretions vary by less than 10% in normal children [6, 7] and knowledge of several accurate 24-h creatinine values enabled an estimate of urine volume (within 10–15%) to be made in those collections from which some urine was lost. In all children a parent was in constant attendance at the bedside and provided reliable information on the completeness of 24-h urine collections.

Sydney water contains sodium fluoride 1 mg litre^{-1} ($50\text{ }\mu\text{mol litre}^{-1}$). Before surgery in the children studied, urinary concentrations of F^{-} varied from 15 to $87\text{ }\mu\text{mol litre}^{-1}$ (mean $42\text{ }\mu\text{mol litre}^{-1}$). This large variation in F^{-} excretion in urine made the estimation of F^{-} ion production from halothane metabolism difficult to assess. In children, 50–60% of an administered dose of F^{-} is absorbed by bone and teeth [8–10]. In the calculation of F^{-} production from halothane metabolism, several assumptions were made. It was assumed that F^{-} in solid food constituted 25% of the total oral F^{-} intake [9]. The second assumption was that 50% of the F^{-} from oral intake and halothane metabolism was excreted in the urine. No account was taken of F^{-} loss in sweat, faeces and wound drainage because losses

from these sites are small. Post-operation urinary Br^{-} values were corrected for the normal daily excretion of Br^{-} determined in each patient before operation.

Urinary half-life of TFA

For each patient the natural logarithm of daily TFA excretion was plotted against time and the slope of the graph measured. Urinary half-life ($T_{1/2}$) of TFA was calculated from the formula:

$$T_{1/2} = \frac{-\text{Log}_e 2}{\text{Slope}}$$

Statistical analysis

The mean, SEM and the 95% confidence interval of the mean for urinary TFA $T_{1/2}$ were calculated from:

$$\bar{x} = \frac{\sum x}{n}$$

$$\text{SEM} = \sqrt{\frac{\sum (x - \bar{x})^2}{n}}$$

$$\mu = \bar{x} \pm \text{SEM}$$

where x = individual patient TFA $T_{1/2}$; $\bar{x}$ = mean TFA $T_{1/2}$; Σ = sum of individual values; n = number of observations; SEM = standard error of the mean; μ = confidence interval of the population mean; and the t -value (95% confidence value) for six degrees of freedom is 2.447.

Analytical methods

Halothane measurements. Halothane was measured using a Hewlett-Packard 5730A gas chromatograph and a flame ionization detector maintained at 250°C . A $1.5\text{-m} \times 2.5\text{-mm}$ Porapak Q (Alltech) 80–100 mesh column maintained at 160°C was used. The carrier gas was nitrogen at a flow rate of 60 ml min^{-1} . Gas samples were withdrawn into 50-ml gas-tight glass syringes. In addition to the standard injection ports, an additional injector consisting of a 10 position Valco valve fitted with a 10-ml gas sample loop was mounted externally to the column oven and connected to the column with $2.7\text{ mm (o.d.)} \times 2.1\text{ mm (i.d.)}$ stainless steel tubing via a 2.7-mm to 5.5-mm Swagelok union allowing 10 ml of gas at atmospheric pressure and room temperature to be injected. The injector loop was flushed with 20 ml of gas sample immediately before injection. A fresh 1% v/v halothane standard was prepared each day. Calibrated conical flasks of 1.0–1.1 litre

volumes were fitted with a short piece of plastic tubing and three-way tap using Parafilm. The calculated quantity of halothane for a 1% v/v standard (halothane 43.9 $\mu\text{l/litre}$ of air at 20 °C) was injected through the Parafilm and allowed 2 min to evaporate. A 25-ml gas sample was withdrawn immediately and injected into the gas chromatograph. Five separate flasks of the 1% v/v halothane standard were prepared and a coefficient of variation between the flasks of less than 5% was obtained. Dilutions of the 1% v/v standard were prepared using two glass syringes and a three-way tap. For a 1 in 10 dilution, a 5-ml syringe containing 1% v/v halothane was transferred to a 50-ml syringe which was filled to the 50-ml mark with air. Peak heights of halothane on the gas chromatograph were linear with concentrations from 1% v/v to 0.001% v/v halothane. The reproducibility of measuring inspired halothane (approximately 1% v/v) was better than $\pm 0.005\%$ v/v.

Trifluoroacetic acid and bromide measurement. TFA (Sigma, St Louis, Missouri) and bromide were measured as methyltrifluoroacetate and methylbromide by a modification of the method of Mariorino, Gandolfi and Sipes [11] using a gas chromatograph with an electron capture detector in place of the mass spectrometer. A 1.0 m $\times$ 2.5 mm i.d. glass column packed with Porapak Qs (Alltech) was used. Column temperature was 135 °C and the flow rate of 5% methane-in-argon carrier gas was 35 ml min⁻¹. TFA and bromide were isolated and measured separately because of their different recoveries and sensitivities.

TFA analysis. To 300 μl of a freshly prepared ice-cold mixture of methanol (1 part) and concentrated sulphuric acid (5 parts) in an uncapped glass vial, 50 μl of urine was added. The mixture was placed immediately in a gas-tight glass syringe containing a 50-ml air space and incubated at 37 °C overnight. A 15-ml headspace sample was removed from the gas-tight syringe and injected through the 10-ml sample injection loop of the gas chromatograph. Recovery of methyl-TFA from urine was $89 \pm 6\%$ and peak heights were linear with initial TFA concentration from 0.2 to 3.0 mmol litre⁻¹.

Bromide analysis. To 300 μl of a freshly prepared ice-cold mixture of methyl sulphate (1 part) and concentrated sulphuric acid (5 parts) was added 50 μl of urine diluted 1:1 with either bromide standard 250 $\mu\text{mol litre}^{-1}$ or water. The vials were immediately crimp-sealed with Teflon-

lined caps and incubated at 37 °C for 2 h. A 1.0-ml headspace sample was withdrawn and injected through the standard injection port of the gas chromatograph. Recovery of methyl bromide from urine was variable, apparently because of further reaction of methyl bromide with other urine constituents. Recovery was improved by further dilution of the sample with water. The recovery for each sample was determined and the Br⁻ result corrected for recovery. Samples giving poor recoveries below 50% were repeated using further 1:2 or 1:4 dilutions in water. Peak height of methyl bromide was linear with bromide concentration from 20 to 250 $\mu\text{mol litre}^{-1}$.

Fluoride, chloride and creatinine measurements. Fluoride was measured using the Radiometer F1052F fluoride selective electrode and K 401M reference electrode attached to a Radiometer pH M84 research pH meter. Urines and suitable dilutions of O.I.M. F⁻ standard (Radiometer) were diluted 1 in 2 with sodium phosphate 1 mol litre⁻¹ buffer, pH 5.0; pF (negative logarithm of the F⁻ concentration) was linear with mV readings in the range fluoride 10⁻⁶–10⁻¹ mol litre⁻¹. Recovery of fluoride 10⁻⁴ mol litre⁻¹ from five spiked urine samples was 95–99%. Chloride was measured with a Bechmann E-4-4 clinical analyser using an ion selective electrode. Creatinine was measured by the Cobas Mira random access analyser using the modified Jaffe reaction.

RESULTS

Uptake of halothane following the administration of 1% halothane for 1 h varied from 176 to 310 mg kg⁻¹ (mean 245 mg kg⁻¹) (table II). Minute ventilation ($\dot{V}$) was not standardized between patients. The youngest three children had the largest $\dot{V}$ kg⁻¹ and the greatest halothane absorption relative to weight. There was an insufficient number of patients to determine the separate influence of age and minute ventilation on halothane uptake. Rate of uptake was greatest during the first 5 min of administration, but had declined to 50% of this rate by 15 min. The rate of uptake then remained almost constant until the conclusion of administration of halothane. For example, patient No. 2 absorbed 661 mg in the initial 5 min of halothane administration, 350 mg in the 5-min period between 15 and 20 min and 330 mg between 55 and 60 min.

TABLE II. Halothane uptake data. FE_{hal} = Concentration of halothane in mixed expired gas. FI_{hal} = Concentration of halothane in inspired gas. † Surgery proceeded faster than anticipated, necessitating a 5-min reduction in halothane administration, from 60 to 55 min. § Because of a faulty vaporiser calibration, the inspiratory halothane concentration in this patient was 0.77%

Patient No.	Tidal volume (ml kg ⁻¹)	Ventilatory rate (b.p.m.)	Minute ventilation (ml kg ⁻¹ min ⁻¹)	Halothane absorption		FE_{hal}/FI_{hal} after 1 h of halothane
				(g)	(mg kg ⁻¹)	
1†	12.1	25	312	2.62	270	0.85
2	13.0	20	260	4.66	310	0.80
3§	11.7	22	257	3.43	236	0.80
4	5.4	20	107	5.00	176	0.73
5	9.5	20	190	9.68	271	0.75
5	7.1	20	142	7.36	226	0.75
6	8.6	20	172	8.92	226	0.78

TABLE III. Halothane elimination data after the administration of halothane was discontinued. * Expired collections continued for only 16 min after the halothane vaporizer was turned off

Patient No.	Minute volume (ml kg ⁻¹ min ⁻¹)	Mixed expired halothane concn (volume %)			Halothane expired (% of uptake)		
		15 min	60 min	90 min	15 min	60 min	90 min
2	260	0.102	0.020	0.011	15	29	32
3	257	0.096	0.016	0.0096	21	33	37
5*	190	0.093	—	—	14	—	—
6	172	0.112	0.028	0.017	14	31	35

Expired halothane excretion

In four patients, expired breath collections were continued after the halothane vaporizer was turned off (table III). The duration of this collection was determined by the surgery and varied from 16 to 100 min. Of the absorbed halothane, 32–37% had been expired 90 min after administration of halothane ceased. Expired concentrations reached MAC awake values [12] 5–6 min after halothane administration was stopped. At this time less than 5% of the absorbed halothane had been expired.

Urinary excretion of halothane metabolites

Urinary excretions of TFA, Br⁻, F⁻ and Cr are given in table IV. Of the absorbed halothane, 11.4% (range 6.3–18.2%) was excreted as TFA. The urinary $T_{1/2}$ of TFA was 41.8 (SD 15.5) h. Assuming the adult $T_{1/2}$ of Br⁻ of 14 days (the half-life of Br⁻ in children is unknown), 4.5% (range 1.9–6.6%) of the absorbed halothane was metabolized to Br⁻. The percentage of absorbed halothane metabolized to urinary F⁻ was 0.37% (range 0.10–0.64%). The ratio of F⁻:TFA was 0.033 (range 0.011–0.067). There was no correlation between age and F⁻ production or between TFA production and F⁻ production.

Patient with liver disease

In this patient, 9.6% of the absorbed halothane was metabolized to TFA, indicating that this degree of liver disease did not diminish the ability of the liver to biodegrade halothane via the oxidative pathway. Of the absorbed halothane, 0.64% was metabolized to urinary F⁻, suggesting that arterial hypoxaemia promotes the reductive metabolism of halothane. This increased reductive metabolism was not associated with deterioration in liver function. Changes in liver function tests comparing preoperative values and values taken 4 days after surgery were: aspartate aminotransferase 19 to 21 u. litre⁻¹; alanine aminotransferase 26 to 31 u. litre⁻¹; gamma glutamyl transpeptidase 31 to 13 u. litre⁻¹; serum bilirubin both values less than 10 µmol litre⁻¹. All results were within the normal range.

DISCUSSION

In 1981 Resurreccion and colleagues [13] measured serum Br⁻ after halothane anaesthesia in 26 children aged from 6 days to 26 months. The increase in serum Br⁻ values were less than those reported previously in adults. Peak serum concentrations occurred at 12–24 h after anaesthesia

TABLE IV. Urinary metabolites of halothane. * It was assumed that 50% of F^- produced from halothane metabolism was absorbed into bone. The values shown are double the amount measured in urine. † The urinary half-life of Br^- was assumed to be 14 days. TFA = Trifluoroacetic acid

Patient No.	Post op. urine collection (days)	Total F^- produced from halothane metabolism* (mmol)	Absorbed halothane metabolized to F^- (%)	Total Br^- produced from halothane metabolism (mmol)	Absorbed halothane metabolized to Br^- (%)	Total TFA excretion (mmol)	Absorbed halothane metabolized to TFA (%)	TFA $T_{1/2}$ (h)
1	3	0.031	0.23	0.11	5.5	0.84	6.28	10.4
2	8	0.150	0.63	0.38	5.5	2.92	12.34	44.8
3	7	0.036	0.21	0.33	6.6	2.04	11.72	54.3
4	4	0.120	0.51	0.17	3.6	4.62	18.20	52.6
5	7	0.110	0.29	0.20	1.9	4.65	12.45	59.1
5	7	0.052	0.10	0.60	4.3	4.55	9.25	31.2
6	7	0.29	0.64	0.53	4.0	4.33	9.56	40.4
Mean (SD)			0.37 (0.20)		4.5 (1.4)		11.4 (3.4)	41.8 (15.5)

as opposed to 72 h in adult patients. Rehder and colleagues [14] studied the biotransformation of halothane in two adult patients. On the basis of TFA excretion, they calculated that 11.6% and 12.0% of the absorbed halothane was metabolized. Using urinary Br^- excretion, they calculated that 20% and 17% of the absorbed halothane was metabolized. Sakai and Takaori [15] studied biodegradation of halothane in five adult patients anaesthetized with halothane for 1 h by measuring uptake and fluoride excretion in urine. These authors found that 17.7% of absorbed halothane was metabolized.

The aim of our study was to confirm or deny the hypothesis that the rate of halothane metabolism and the proportion of absorbed halothane metabolized differs between children and adults. Halothane uptake in our study is in good agreement with that from previous studies in children [16, 17]. After ventilation of the subjects' lungs with 1% halothane for 60 min, uptake varied from 176 to 310 mg kg^{-1} , depending on $\dot{V}$. Theoretically, oxidative metabolism of halothane releases TFA and Br^- in equimolar proportions, but in our study there was little correlation between TFA and Br^- production. Of the absorbed halothane, 11.4% (range 6–18%) was excreted in urine as TFA. Based on urinary Br^- excretion, a biological $T_{1/2}$ of Br^- of 10–14 days [18, 19], normal hydration and normal mineral metabolism, 4.5% (range 1.9–6.6%) of the absorbed halothane was metabolized.

Bromide balance studies in children after major surgery provide an inaccurate index of the percentage of absorbed halothane which is metabolized. Initially, after surgery in the patients studied, urinary excretion of Cl^- and Br^- was low, indicating salt conservation to restore a depleted extracellular volume. Excretion of Br^- is influenced by hydration and anion balance, as Br^- and Cl^- have similar distribution patterns in the extracellular fluid and compete for renal tubular reabsorption [20, 21]. A study in rats [22] found that Br^- $T_{1/2}$ varied from 2.5 days during high Cl^- intake to 25 days during low Cl^- intake. On the other hand, TFA has a half-life of 2 days, does not occur in nature and has a urinary excretion which is little affected by fluid and electrolyte balance. Measurement of urinary TFA provides a more reliable assessment of the oxidative metabolism of halothane than does measurement of urinary Br^- .

Of the absorbed halothane, 0.37% (range 0.10–0.64%) was metabolized via a reductive

pathway [23] to urinary F^- . Two earlier adult studies [14, 15] found that approximately 0.1% of absorbed halothane was metabolized to urinary F^- . The F^- produced from halothane metabolism forms a small fraction of total urinary F^- excretion, making estimation of the reductive metabolism of halothane by measuring fluctuations of urinary F^- inaccurate. Fluid and food fluoride intake, bone absorption, fluid and electrolyte balance, urine flow and urine pH affect urinary F^- excretion [24]. Even allowing for the inherent inaccuracies involved in using urinary F^- to reflect reductive metabolism, the children in our study metabolized as much, or more halothane via the reductive pathway than did adult patients reported in previous studies [14, 15].

The average urinary half-life of TFA following halothane anaesthesia in our study was 42 h (95% confidence interval 26–57 h). In two adult patients [14] the urinary $T_{1/2}$ of TFA was 61 and 63 h. This suggests that children metabolize halothane faster than adults, but statistical comparison between the two studies was not attempted because of the small number of results available for analysis.

Cohen and colleagues [25] gave radiolabelled halothane to eight patients and identified three major urinary metabolites of halothane: N-trifluoroacetyl-2-aminoethanol, N-acetyl-S-(2-bromo-2-chloro-1,1-difluoroethyl)-cysteine and TFA. Earlier studies [26] found TFA as the only detectable metabolite. In our study, TFA was the only organofluoride halothane metabolite measured in urine. It is possible that, by failing to identify and measure other organofluoride metabolites of halothane, our study underestimates halothane metabolism.

Studies in adults using radiolabelled halothane, in which urine was collected for up to 14 days, indicate that 5–25% of absorbed halothane is metabolized [26, 27]. Carpenter and colleagues [28] studied halothane metabolism in nine adults without measuring urinary metabolites. Halothane recovered in exhaled gases sampled for up to 9 days after operation was compared with the amount absorbed during anaesthesia. The authors found that 46% of absorbed halothane was metabolized—twice that reported by all other workers. However, there were deficiencies in the measurement of $\dot{V}$ which may have lead to overestimation of halothane metabolism. In addition, 0.226% inspired halothane was used, as opposed to the 1% halothane in our study. A greater fraction of halothane taken up at sub-

anaesthetic as opposed to anaesthetic concentrations is metabolized [29], and this may partly explain the differences found between the two studies in the percentage of absorbed halothane which is metabolized.

Both the oxidative and reductive metabolic pathways of halothane have been implicated in causing hepatic injury after halothane anaesthesia [23, 30]. Our study has demonstrated that there are no major qualitative or quantitative differences between children and adults in their ability to metabolize halothane via either the oxidative or reductive pathways. The observed difference in incidence of halothane associated hepatitis between children and adults was not explained by our study of halothane metabolism in normal children.

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BIOTRANSFORMATION AND HEPATO-RENAL FUNCTION IN VOLUNTEERS AFTER EXPOSURE TO DESFLURANE (I-653)

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SUMMARY

Ten healthy unpremedicated male volunteers were exposed to an average inspired concentration of 3.6% desflurane (I-653) in oxygen for 89 (SD 17) min. Standard haematological and biochemical tests were performed before (control) and immediately after exposure and at 4, 24, 72 and 192 h. Liver function was assessed at these times by determining total and unconjugated (indirect) bilirubin, and plasma concentrations of aspartate amino transferase, alanine amino transferase, γ -glutamyl transpeptidase and alkaline phosphatase. Renal function was assessed by examining the urine microscopically for leucocytes, red blood cells, casts and crystals at these times, and creatinine clearance and urine concentrating ability were determined before and 24 and 72 h after exposure. Two additional and sensitive tests of renal integrity were performed before and 4 and 24 h after anaesthesia: measurement of urinary retinol-binding protein and β -N-acetyl-D-glucosaminidase. Serum inorganic fluoride was determined immediately before and 1, 4, 24, 48, 72 and 192 h after anaesthesia. Urinary inorganic and organic fluoride concentration and excretion rate were determined before and 24, 48, and 72 h after anaesthesia. There were no significant changes in any measured haematological or biochemical variable (other than an increase in total white cell count from 5.9 (1.3) to 8.3 (1.1) $\times 10^9$ litre⁻¹ immediately after exposure) nor in liver or renal function tests. There was no increase in serum or urinary inorganic fluoride or urinary non-volatile organic fluoride concentrations.

KEY WORDS

Anaesthetics volatile: desflurane (I-653). Biotransformation: fluorometabolites. Kidney: function. Liver: function.

The new inhalation anaesthetic, desflurane (I-653), is a methyl ethyl ether halogenated only with fluorine. It has a molecular weight of 168 Da, a boiling point of 23.5 °C and a vapour pressure of 644.3 mm Hg at 20 °C. Its stability appears to equal or exceed that of all potent inhaled agents in clinical use [1-3]. Results of studies in rats suggest that it is free from hepatic and renal toxicity [4, 5]. Serum or urinary inorganic and organic fluoride concentrations do not increase significantly, or increases only slightly, in enzyme-induced rats after exposure to desflurane for 2 h at 1.6 MAC [3], and in swine after exposure at 5.5 MAC-h there was no detectable increase in serum concentration of fluoride immediately after anaesthesia and a 17% increase after 4 h; this compares with a three-fold increase at comparable times following 5.5 MAC-h exposure to isoflurane [6].

We investigated hepatic and renal function and standard haematological and biochemical indices after exposure of healthy male volunteers to desflurane. We also measured biotransformation

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TABLE I. *Standard haematological tests*

Red Cells	White cells (% of total and count)	Microscopy
Haemoglobin	Neutrophils	Platelet count
Red cell count	Lymphocytes	Kaolin partial thromboplastin time
Packed cell volume	Monocytes	Prothrombin time
Mean corpuscular volume	Eosinophils	
Mean corpuscular haemoglobin	Basophils	
Mean corpuscular haemoglobin concentration		
Erythrocyte sedimentation rate		

as defined by changes in concentrations of serum and urinary inorganic fluoride and total urinary organic fluoride.

SUBJECTS AND METHODS

Eleven healthy male volunteers were studied after obtaining institutional Ethics Committee approval and written informed consent. The first four volunteers were department members (who had not worked in an operating theatre environment for at least 3 days before exposure to desflurane) and most of the remainder were medical students. No volunteer had been anaesthetized in the previous 12 months, none had smoked for at least 5 yr and none had taken any medications for at least 2 weeks before the study. We excluded volunteers who had a history of significant disease, a positive Australia antigen result, or an illicit drug history. A full physical examination was performed. Urine microscopy, fundoscopy, oral temperature, electrocardiography and standard haematological and biochemical tests were undertaken also (tables I, II). Before exposure to desflurane, volunteers abstained from alcohol and caffeine-containing drinks for 48 h and all were admitted to Guy's Hospital on the afternoon before study. Department members were kept in hospital overnight after the study and all other volunteers were kept in the Clinical Research Unit until completion of all investigations (7 days). Thus collection of all specimens, including 24-h urine samples, could be guaranteed.

Volunteers were unpremedicated and exposed only to desflurane in oxygen. Before exposure to desflurane an i.v. infusion of Hartmann's solution $3 \text{ ml kg}^{-1} \text{ h}^{-1}$ was started and continued throughout the study until the subject was taking oral fluids freely. A sampling cannula was sited in the arm opposite to that used for the infusion. We exposed the first volunteer (one of the investi-

TABLE II. *Standard biochemistry tests*

Serum osmolality	Calcium
Sodium	Phosphorus
Potassium	Creatine phosphokinase (total)
Chloride	Creatine phosphokinase (M.B. fraction)
Bicarbonate	Total proteins
Urea	Albumin
Creatinine	Globulin
Uric acid	Cholesterol
Glucose	Triglycerides

gators, J.N.C.), to subanaesthetic concentrations of the agent for approximately 1 h and demonstrated lack of toxicity at this concentration before exposing the remaining volunteers to anaesthetic concentrations of the agent. Immediately before exposure to desflurane, volunteers emptied their bladders. The agent was breathed via a clear plastic cuffed mask attached by a corrugated Teflon tube to an anaesthetic breathing system containing soda-lime for absorption of carbon dioxide. Inspired and expired desflurane concentrations were measured by Datex Multigas analysers, modified to measure desflurane, which were calibrated before and after each study with gravimetrically prepared gases containing 1.5, 3.0 and 6.0% desflurane. The anaesthetic was delivered by a modified Ohio DM 5000 anaesthetic machine with an electrically heated, temperature controlled vaporizer (direct metering vaporization). During the study period subjects were monitored using a 12-lead ECG, frequent (at least 5-min intervals) arterial pressure measurement and pulse oximetry. The first six subjects were exposed initially to 1.8% inspired desflurane for 30 min and the second five subjects were exposed initially to 5.4% inspired agent for the same period of time. In all subjects the inspired concentration was increased until there was no response to a standard painful stimulus (tetanic stimulation of the ulnar nerve for 30 s using a

supramaximal stimulus)—that is, until they were anaesthetized.

Assessment of liver function

Serum concentrations of total and unconjugated (indirect) bilirubin were measured before (control) and immediately after exposure to desflurane (0 h) and at 4, 24, 72 and 192 h after exposure. Concentrations of the following liver enzymes in serum were measured also at these times: aspartate amino transferase (AST) and alanine amino transferase (ALT) (these are known also by the products of the reaction rather than by the amino-group donor as glutamic and oxalo-acetic, and glutamic and pyruvic transaminase (SGOT and SGPT, respectively); alkaline phosphatase, which catalyses the release of inorganic phosphate from a phosphate ester substrate; γ -glutamyl transpeptidase, which is an enzyme that increases in circumstances which induce liver microsomal enzymes (e.g. consumption of alcohol).

Assessment of renal function

Urine was examined microscopically for leucocytes, red blood cells, casts and crystals at the screening visit and 4, 24, 72 and 192 h after anaesthesia. To determine creatinine clearance, urine and plasma concentrations of creatinine were measured together with urine volume. This was done before exposure to desflurane and 24 and 72 h after exposure. Urine concentrating ability was determined also at these times. Two other tests of renal function were performed before exposure (control) and 4 and 24 h after exposure: measurement of urinary retinol-binding protein and β -N-acetyl-D-glucosaminidase—each a sensitive indicator of drug-induced renal damage. Retinol-binding protein (RBP) is a low molecular weight (21 000 Da) protein bound largely to pre-albumin. The unbound fraction is filtered at the glomerulus and then reabsorbed totally in the proximal convoluted tubule. Excretion of this low molecular weight protein indicates impairment of tubular function. β -N-acetyl-D-glucosaminidase (NAG) is a lysosomal enzyme with a molecular weight of 150 000 Da. Its size precludes filtration through the normal glomerulus. This enzyme exists in high concentration in renal tubules and increased NAG activity in urine indicates leakage of lysosomal enzymes and nephrotoxic damage.

Serum and urine inorganic fluoride and urinary non-volatile organic fluoride

Serum was analysed for inorganic fluoride before (control) and at 1, 4, 24, 72 and 192 h after

anaesthesia. Urinary concentration and excretion rate of organic and inorganic fluoride were determined before (control) and 24, 48 and 72 h following anaesthesia, by the method of Fry and Taves [7]. Briefly, thawed serum and urine samples were centrifuged at 10 000 *g* for 3 min to remove particulate matter. Twenty microlitre of sodium acetate buffer 5 mol litre⁻¹ (pH 4.5) was added to undiluted serum 180 μ l or to 180 μ l of a urine sample, typically diluted 10-fold. The 200- μ l mixture was placed into a machined Teflon cup and fluoride ion concentration was measured using an Orion fluoride ion electrode (model 96-09) with a Corning model 12 pH meter or a Corning 150 ion analyser. Fluoride ion concentrations in serum or urine were obtained by interpolation of a calibration curve prepared by plotting mV values on a linear scale against concentration of sodium fluoride standards on a logarithmic scale. Sodium calibration curves were obtained with the use of distilled water or in the presence of control serum or urine. The urine was analysed also for non-volatile organic fluoride by the sodium fusion method of Stoltis and Gandolfi [8]. Organic fluoride from urine samples was calculated by subtracting the free fluoride ion in the original sample from the total fluoride content determined by the sodium fusion technique, after correction for the efficiency of organic fluoride detection in urine ($90.4 \pm 18.3\%$; $n = 25$).

All data are reported as mean (SD). Measured data were analysed by one-way analysis of variance and paired *t* test with a Bonferroni correction as applicable.

RESULTS

The first volunteer was exposed to an appreciably lower (1.8% inspired) concentration of the agent for a shorter period (1 h) than the other volunteers and thus the data from this subject (which were unremarkable) were not included with those of the remaining 10 subjects. The latter were exposed to desflurane for 89 (17) min at an average concentration of 3.6% inspired (range 1.8–6.2%). Haematological and biochemical tests before and after exposure were unremarkable and, with the exceptions detailed below, any small changes after anaesthesia could be explained in terms of the period of fasting which participation in the study entailed.

The white blood cell count increased significantly ($P < 0.01$) immediately after exposure from $5.9 (1.3) \times 10^9$ litre⁻¹ to $8.3 (1.1) \times 10^9$ litre⁻¹,

TABLE III. Renal function tests (mean (SD)) (n = 10). RBP = Retinol binding protein; NAG = β -N-acetyl-D-glucosaminidase

	Control	Time after test drug (h)				
		0	4	24	72	192
Plasma urea (mmol litre ⁻¹)	5.8 (1.7)	5.2 (1.2)	4.8 (1.2)	4.7 (1.0)	4.7 (1.2)	5.2 (1.5)
Plasma creatinine (μ mol litre ⁻¹)	97 (17)	97 (17)	88 (17)	88 (17)	97 (17)	88 (17)
Creatinine clearance (ml min ⁻¹)	136 (32)	—	—	138 (28)	145 (19)	—
RBP (μ g/mmol creatinine)	6.8 (2.5)	—	5.9 (2)	7.4 (3.3)	—	—
NAG (μ mol para-nitrophenol h ⁻¹ /mmol creatinine)	19 (4)	—	24 (10)	23 (11)	—	—

but returned to $6.0 (1.2) \times 10^9$ litre⁻¹ after 4 h and remained unchanged thereafter. The increased value immediately after exposure is within the normal range for our laboratory ($4-11 \times 10^9$ litre⁻¹).

Two subjects had increased creatine phosphokinase (CPK) concentrations both before and after exposure to the test drug. One had a value of 328 iu litre⁻¹ at the screening test (normal range for our laboratory 24-195 iu litre⁻¹) and values of 389, 353, 178 and 264 iu litre⁻¹ at 4, 24, 72 and 192 h, respectively, after exposure. Another had a value of 369 iu litre⁻¹ at the screening test and 338, 209, 108 and 1093 iu litre⁻¹ at 4, 24, 72 and 192 h, respectively, after exposure. Both subjects were young men engaged in athletic activities and, because they had no other abnormal data, we concluded that these increased values represented increases which are seen after muscular activity. In isolation, the data did not warrant excluding

the subjects from the study. Triglyceride values, both before and after the trial, were also slightly increased in some subjects on some occasions. Again, when occurring in isolation before the study, this was not considered sufficient to warrant exclusion of the subject from the trial.

Urinary microscopy did not reveal abnormalities at any time after exposure, and urinary concentrating ability was maintained at 24 and 72 h (sp.gr. 1015 control; 1020 at 24 h; 1020 at 72 h). Renal function tests were unchanged by exposure to desflurane (table III). Liver function tests also were unchanged by exposure to desflurane (table IV).

Serum and urinary fluoride ion and non-volatile urinary organic fluoride concentrations did not change (table V). Urinary fluoride excretion rate increased significantly ($P = 0.0057$) for the first 24 h and the increase in organic fluoride excretion rate approached significance ($P = 0.033$).

TABLE IV. Liver function tests (mean (SD)) (n = 10)

	Control	Time after test drug (h)				
		0	4	24	72	192
Total bilirubin (μ mol litre ⁻¹)	12.0 (8.5)	13.7 (3.4)	13.7 (3.4)	10.3 (3.4)	10.3 (5.1)	12.0 (3.4)
Unconjugated bilirubin (μ mol litre ⁻¹)	10.3 (6.8)	12.0 (3.4)	10.3 (3.4)	8.5 (6.8)	8.5 (5.1)	8.5 (3.4)
Alanine amino-transferase (u litre ⁻¹)	18 (6)	19 (7)	17 (6)	17 (6)	20 (9)	20 (9)
Aspartate amino-transferase (u litre ⁻¹)	24 (6)	22 (5)	21 (5)	22 (5)	24 (5)	28 (7)
Alkaline phosphatase (u litre ⁻¹)	71 (11)	76 (15)	76 (13)	73 (13)	78 (14)	74 (12)
γ -glutamyl transpeptidase (u litre ⁻¹)	16 (6)	16 (6)	16 (6)	16 (6)	12 (4)	15 (6)

TABLE V. Fluoride concentrations and excretion rates (mean (SD)) (n = 10). Values for urine for 24, 48 and 72 h are for 24-h collections. †0.44 (0.31) $\mu\text{mol litre}^{-1}$ at 192 h

	Control	Time after administration of anaesthetic (h)				
		1	4	24	48	72
Fluoride concns ($\mu\text{mol litre}^{-1}$)						
Serum F ⁻ †	0.79 (0.56)	0.46 (0.29)	0.62 (0.30)	0.36 (0.17)	0.30 (0.11)	0.45 (0.31)
Urine F ⁻	29 (14)			24 (8)	22 (11)	18 (7)
Urine organic F	86 (19)			75 (14)	70 (19)	79 (12)
Urine fluoride excretion rates ($\mu\text{mol h}^{-1}$)						
Inorganic F	1.2 (0.5)			1.5 (0.4)	1.3 (0.7)	1.4 (0.6)
Organic F	3.9 (1.5)			5.1 (1.5)	4.2 (1.5)	6.4 (1.9)
Total F	5.1 (1.6)			6.7 (1.5)	5.5 (1.5)	7.8 (2.1)

DISCUSSION

The molecular structure of desflurane differs from that of isoflurane only in the substitution of fluorine for chlorine at the alpha ethyl carbon. It has a physical stability equal to or more than that of isoflurane in terms of their relative degradation in soda-lime of varying temperature and water content [1, 2]. This molecular stability suggests that desflurane undergoes minimal biotransformation. Indicators of the degree of biotransformation of fluorinated anaesthetics include the serum and urinary concentrations of fluoride ions and total urinary organic fluoride concentrations. Koblin and colleagues [3] have investigated the biotransformation of methoxyflurane, halothane, isoflurane and desflurane in rats pretreated with phenobarbitone in a series of controlled experiments. There were very marked (up to a 100-fold) increases in plasma and urinary fluoride ions and urinary organic fluoride concentrations in rats exposed to halothane and methoxyflurane, whereas isoflurane caused a measurable but smaller increase. The concentrations of fluoride after desflurane were virtually indistinguishable from those of the control animals. Similarly, in swine exposed to approximately 5.5 MAC-h of isoflurane or desflurane, plasma concentrations of fluoride ion were three times greater than control values immediately after and at 4 h after exposure to isoflurane, whereas there was no detectable increase immediately after anaesthesia with desflurane and only a 17% increase after 4 h [6]. The foregoing animal data suggest that desflurane is biotransformed significantly less than all existing halogenated anaesthetic agents. Our data indicate

that, at the exposures in this study, desflurane was also minimally biotransformed in man. Volunteers were exposed to no other drug and received desflurane at concentrations up to 6% for approximately 90 min, the average inspired concentration being 3.6%. The data concerning the potency of desflurane in dogs, rabbits and rats, together with previous studies of comparative potency, suggest that the projected human MAC is about 5.1% [9]. Thus the volunteers were exposed to approximately 1 MAC-h of desflurane. This exposure produced no measurable increase in serum fluoride ions, urinary fluoride ions and total urinary concentration of organic fluoride. There was a slight, but measurable, increase in excretion rate of urinary fluoride ion. However, this was related probably to the relative diuresis which occurred after allowing volunteers to drink freely after exposure to desflurane which had been preceded by a 15-h fast.

Various studies have examined the potential of desflurane to cause toxicity in animals. Eger, Johnson and Ferrell [4] subjected rats to six, 2-h exposures of 1.6 MAC isoflurane or desflurane in a controlled study and reported that no tissue damage attributable to the anaesthetics occurred and weight gain was not affected. This lack of toxicity extended to an enzyme-induced hypoxic rat model [5]. The animals were pre-treated with phenobarbitone and exposed for 1 h to 12% oxygen and no anaesthesia (control) or to 1.2 MAC halothane, isoflurane or desflurane. Liver, kidney and lung specimens were examined 24 h after exposure. Pulmonary and renal damage was not evident in any of the groups, but the livers of all rats exposed to halothane had marked

swelling and centrilobular necrosis, whereas isoflurane produced only slight injury (20% of rats had minor swelling and centrilobular necrosis) and no damage was discernible in the control or desflurane groups.

Administration of 1 MAC-h of desflurane did not alter any indices of liver or renal function in our volunteers. In addition to the standard tests of liver and renal function, we used two recently developed and very specific indices of renal integrity, namely measurement of urinary RBP and NAG. Increased excretion of NAG is a particularly sensitive index of drug-induced nephrotoxicity [10, 11] and the presence of RBP in urine is considered to be the most specific marker yet developed for tubular damage of any cause [12]. Exposure to desflurane caused no change in the excretion of these proteins. Although we could discern no evidence of hepatic or renal damage, it must be emphasized that our study was limited to an approximately 1 MAC-h exposure in healthy young male volunteers. Although these results in man are consistent with those from animals, a more definite conclusion on the safety of desflurane must await exposure to higher concentrations of the anaesthetic and to larger numbers of subjects, particularly patients with disease states and drug histories.

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MASSETERIC MUSCLE SPASM AS A NORMAL RESPONSE TO SUXAMETHONIUM

N. P. LEARY AND F. R. ELLIS

SUMMARY

The myotonic response of the masseter muscles following various doses of suxamethonium was measured using a unique myotonometer in 50 apparently healthy patients, the majority of whom showed a myotonic response which lasted less than 100 s. A maximum increase in masseter tone was found to be greater than 1 kg in five patients, and 12 patients developed a maximum tone of greater than 500 g. An increased masseter tone of this degree might be interpreted as "masseteric muscle spasm" by the anaesthetist. The value of masseteric muscle "spasm" as an early sign of malignant hyperthermia is questioned.

KEY WORDS

Complications: myotonic. Neuromuscular block: suxamethonium.

Suxamethonium is known as an agonistic neuromuscular blocker, with the ability to produce a rapid and profound loss of muscle tone. Myotonia of the jaw muscles of a marked degree (termed masseter spasm (MS), masseteric muscle spasm (MMS), masseteric muscle rigidity (MMR) or trismus), is recognized as a potential herald for malignant hyperthermia (MH) [1, 2].

Retrospective studies of patients presenting with this feature suggest that about 50% prove to be susceptible to malignant hyperthermia (MHS) [3]. Therefore 50% of referrals with MMS are apparently normal (MHN), although a few show EMG changes consistent with myotonia and so may have one of the myotonic muscle diseases, such as myotonia congenita.

More recently, there have been two studies reporting increasing jaw stiffness with resistance to mouth opening following i.v. suxamethonium [4, 5]. Different populations (children or adults), different induction techniques (inhalation or i.v.)

and different methods of measurement prevent direct comparison, but both of these studies indicate that an increase in the tone of the jaw muscles may be a normal response following suxamethonium. This study presents the results of an investigation into the incidence and degree of change in jaw tone following different doses of suxamethonium in adults after induction of anaesthesia with thiopentone.

PATIENTS AND METHODS

We studied 50 healthy adult patients (ASA I and II) presenting for elective surgery for which general anaesthesia with intubation was appropriate; the study was approved by the local District Ethics Committee. Weight, sex and age of the patients were recorded.

All patients were premedicated with diazepam 10 mg at least 90 min before induction of anaesthesia. Following preoxygenation, a sleep dose of thiopentone was administered i.v. via an indwelling winged needle in the dorsum of the left hand and anaesthesia maintained thereafter with 66% nitrous oxide in oxygen. Additional small increments of thiopentone were given, if the level of anaesthesia became too light as judged by clinical parameters. The 50 patients were allocated to five groups of 10 patients, each receiving a different dose of suxamethonium diluted to a volume of 5 ml with 0.9% saline: 0.25 mg kg⁻¹ (group A); 0.5 mg kg⁻¹ (group B); 0.7 mg kg⁻¹ (group C); 1.0 mg kg⁻¹ (group D); 2.0 mg kg⁻¹ (group E).

The following variables were recorded, using a Devices multichannel recorder and a flat-bed

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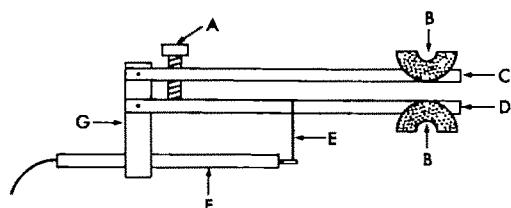


FIG. 1. Myotonometer for masseteric muscle tone measurement. A = Knurled nut for adjusting arm position; B = adjustable plastic grooves to fit bite; C = fixed beam; D = moving beam; E = rigid connection between moving beam and transducer arm; F = isometric force transducer housing; G = rigid frame.

recorder (Phillips PM8251A) which were synchronized:

Jaw tone. A myotonometer was constructed (fig. 1) to fit as a calliper between the upper and lower incisors. One limb of the calliper was made as a torsion beam and attached rigidly to a strain gauge. Before recordings were made, a preload was applied to ensure the calliper limbs were approximately parallel and the teeth separated by approximately 2 cm.

Muscle twitch. Supramaximal stimulation of the ulnar nerve at the elbow using a Bard Biomedical 750 digital transcutaneous peripheral nerve stimulator (square wave of 0.2 s duration at 1 Hz) was used and thumb adduction recorded using a manometer.

Fasciculation. Onset and offset of fasciculations in the jaw, tongue muscles, or both were assessed clinically and recorded using a remote incident marker.

Figure 2 is a diagrammatic representation of the study. Time zero was taken as the end-point of the suxamethonium injection. Measurements included the onset and offset times for fasciculations, the offset time for twitch, the onset, peak and offset times for increase in tone, and the magnitude of the tone change at its peak and at the onset and offset of fasciculations and at 5 and 10 s after each event. The area under the tone curve was calculated.

Laryngoscopy was not attempted until all jaw tone changes had returned to initial resting values.

Demographic data were analysed using a one-way analysis of variance for independent samples. Similarly, the duration of suxamethonium injection and the preload applied were compared between the five groups using one-way analysis of variance for independent samples. Regression analysis was used to compare the five suxamethonium dose groups, with respect to fasciculation onset, offset and duration times; twitch offset time; increased tone onset, offset, peak and duration times; maximum tone; area under curve of tone increase; tone occurring at onset and offset of fasciculation and 5 and 10 s after each event.

Significance was assessed by Student's *t* test.

RESULTS

There were no significant differences between the five groups with respect to age and weight (table I), or duration of injection of suxamethonium and preload (table II).

There were significant negative correlations

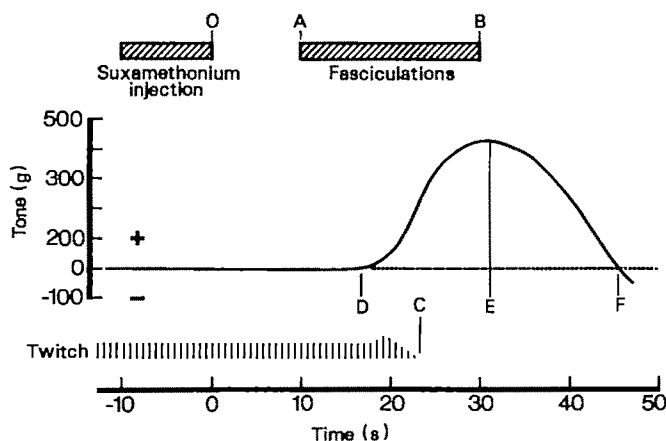


FIG. 2. Diagrammatic representation of study. A-B = Period of observed facial muscle fasciculation; C = cessation of muscle twitch from ulnar nerve stimulation; D = onset of increased muscle tone; E = maximum muscle tone; F = offset of increased muscle tone.

TABLE I. *Details of the five groups of patients (no significant differences)*

	Suxa- methonium dose (mg kg ⁻¹)	Age (yr)	Weight (kg)	Sex (F:M)
Group A	0.25	36.3 (13.3)	67.4 (8.7)	8:2
Group B	0.5	40.8 (11.0)	67.0 (6.7)	10:0
Group C	0.7	33.7 (11.1)	69.4 (12.0)	10:0
Group D	1.0	30.7 (6.6)	60.7 (11.1)	10:0
Group E	2.0	41.7 (13.8)	63.5 (12.6)	10:0

TABLE II. *Mean (SD) duration of injection of suxamethonium and preload applied to the myotonometer in the five groups of patients. No significant differences*

	Suxamethonium dose (mg kg ⁻¹)	Duration of suxamethonium injection (s)	Preload (g)
Group A	0.25	9.1 (2.3)	800 (290)
Group B	0.5	7.2 (2.1)	695 (261)
Group C	0.7	8.0 (2.1)	772 (329)
Group D	1.0	10.2 (2.6)	830 (418)
Group E	2.0	10.0 (3.4)	744 (421)

TABLE III. *Mean (SD) time of onset, offset and duration of fasciculation, and time to complete neuromuscular block (twitch fade) in the five groups of patients*

	Suxamethonium dose (mg kg ⁻¹)	Fasciculation			Twitch fade (s)
		Onset (s)	Offset (s)	Duration (s)	
Group A	0.25	14.7 (7.7)	38.7 (14.3)	23.9 (15.3)	30.2 (16.7)
Group B	0.5	12.2 (2.6)	35.2 (6.3)	23.0 (6.5)	27.8 (12.5)
Group C	0.7	9.7 (2.4)	33.0 (6.9)	23.3 (7.0)	23.6 (6.6)
Group D	1.0	12.2 (4.4)	31.4 (7.2)	19.2 (5.9)	24.3 (12.2)
Group E	2.0	8.1 (2.9)	30.0 (12.2)	21.8 (10.8)	13.5 (5.9)
P		< 0.01	< 0.05	ns	< 0.01

TABLE IV. *Mean (SD) onset, offset, duration and peak times of development of increased tone in the five groups of patients*

	Suxamethonium dose (mg kg ⁻¹)	Positive tone			
		Onset (s)	Offset (s)	Duration (s)	Peak (s)
Group A	0.25	23.3 (13.7)	70.4 (17.6)	50.7 (16.2)	53.0 (15.0)
Group B	0.5	14.8 (6.1)	51.9 (13.1)	38.1 (19.3)	33.3 (7.8)
Group C	0.7	17.0 (5.4)	45.4 (16.0)	27.4 (15.5)	29.9 (7.7)
Group D	1.0	8.0 (6.1)	36.3 (13.6)	28.3 (9.9)	17.6 (9.2)
Group E	2.0	11.2 (4.6)	37.1 (14.7)	25.9 (13.1)	19.6 (5.5)
P		< 0.01	< 0.01	< 0.01	< 0.01

between suxamethonium dose and time of onset of fasciculations, the latter decreasing from 14.7 (SD 7.7) s with group A to 8.1 (2.9) s with group E ($P < 0.01$). Likewise there was a significant negative correlation between dose and offset of fasciculations, the latter decreasing from 38.7 (14.3) s for group A to 30.0 (12.2) s for group E ($P < 0.05$). However, there were no significant differences for the duration of fasciculations between any of the groups (23.9 (15.3) s for group A and 21.8 (10.8) s for group E). There was a significant negative correlation between dose of suxamethonium and the duration of fade for the ulnar twitch, with the latter decreasing from 30.2 (16.7) s for group A to 13.5 (5.9) s for group E ($P < 0.01$) (table III).

The timing of the onset of the increase in jaw tone showed a significant negative correlation with dose of suxamethonium, occurring at 23.3 (13.7) s for group A, but diminishing to 11.2 (4.6) s for group E ($P < 0.01$). Similar significant negative correlations occurred with respect to time of offset 70.4 (17.6) s for group A decreasing to 37.1 (14.7) s for group E ($P < 0.01$), duration of positive tone 50.7 (16.2) s for group A decreasing to 25.9 (13.1) s for group E ($P < 0.01$), and timing of peak tone 53.0 (15.0) s for group A decreasing to 19.6 (5.5) s for group E ($P < 0.01$) (table IV).

TABLE V. Mean (SD) maximum tone deflection and area under the deflection curve in the five groups of patients. No significant differences

	Suxamethonium dose (mg kg ⁻¹)	Positive maximum (g)	AUC (g s)
Group A	0.25	+442 (356)	11.4 (11.7)
Group B	0.5	+454 (540)	12.0 (10.5)
Group C	0.7	+241 (180)	4.9 (3.0)
Group D	1.0	+572 (549)	8.2 (8.3)
Group E	2.0	+457 (501)	4.6 (5.3)

No significant correlation was found between dose of suxamethonium and the magnitude of the increases in jaw tone (442 (356) g for group A and 457 (501) g for group E), or the calculated area under the tone curve (11.4 (11.7) g s for group A and 4.6 (5.3) g s for group E) (table V). Similarly, there were no significant correlations between dose and the tone generated at the three set times related to each of fasciculation onset and offset (table VI). However, in all dose groups approximately 50% of patients were still generating increased tone 10 s after the offset of fasciculation (fig. 3). Figure 4 illustrates the distribution of peak tone values in each of the five groups.

Laryngoscopy was attempted at 60–90 s after the end of suxamethonium injection in all patients. In those requiring repeat suxamethonium, the final laryngoscopy occurred within 3 min of the end of the initial injection of suxamethonium. Six patients in group A and one each in groups B and C required additional suxamethonium for intubation. In the lower dose groups, this was presumed to be a result of inadequate paralysis, whilst in the one patient in group C no change in jaw tone from resting values was detected, but mouth opening proved impossible. Intubation was successful following the second dose of suxamethonium.

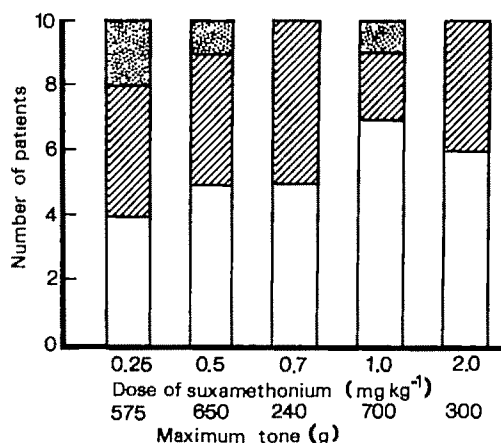


FIG. 3. Distribution of generated tone 10 s after the offset of fasciculations in each of five groups of patients receiving different doses of suxamethonium. □ = No tone; ▨ = 1–499 g; ▩ = 500–999 g. Approximately 50% of patients in each of the different groups was still generating jaw tone.

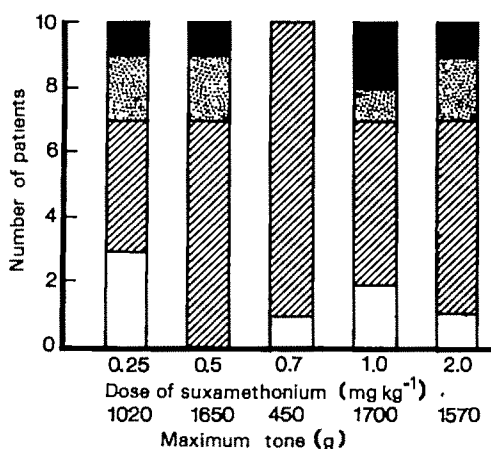


FIG. 4. Distribution of peak tone in each of the five groups of patients receiving different doses of suxamethonium. □ = No tone; ▨ = 1–499 g; ▩ = 500–999 g; ■ = > 1000 g.

TABLE VI. Mean (SD) tone generated at onset of fasciculation (F0), 5 s later (F5) and 10 s later (F10), and similarly at the offset of fasciculations (Fe0), 5 s later (Fe5) and 10 s later (Fe10), in the five groups of patients. No significant differences

	Suxamethonium dose (mg kg ⁻¹)	F0	F5	F10	Fe0	Fe5	Fe10
Group A	0.25	-34 (81)	-20 (57)	0 (57)	125 (21)	+126 (272)	+109 (236)
Group B	0.5	-9 (30)	+5 (88)	+278 (527)	+217 (268)	+149 (255)	+141 (229)
Group C	0.7	-28 (69)	-31 (104)	+47 (264)	+105 (561)	+47 (583)	-2 (616)
Group D	1.0	+229 (463)	+311 (511)	+463 (514)	+177 (245)	+121 (221)	+106 (243)
Group E	2.0	-1 (30)	+52 (140)	+182 (215)	+115 (148)	+100 (150)	+62 (99)

No patient developed any sign of hypermetabolic state as indicated by cardiovascular, temperature and end-tidal carbon dioxide monitoring.

DISCUSSION

Suxamethonium was first used in humans in 1951 [6, 7]. It is surprising that the observation that this drug has myotonic properties has been so delayed, especially as generations of anaesthetists have used suxamethonium as an important part of the rapid induction sequence. In the knowledge of the results of this study, it is tempting to suggest that intubation is achieved in these circumstances under the influence of thiopentone and before the suxamethonium-induced masseteric spasm has occurred. Delayed intubation resulting from inexperience could result in worsening conditions until the masseteric spasm has worn off and tone returned to baseline after about 60–90 s. The best time for intubation, provided suxamethonium 0.7–1.0 mg kg⁻¹ is given, is 20–30 s after cessation of facial fasciculations.

From this study it would appear that the increase in masseter muscle tone after suxamethonium is distributed normally. It can be predicted from the standard deviation statistics that one patient in every 20 may show a masseteric muscle tone increase of greater than 1500 g, and one patient in every 100 may show an increase greater than 2000 g. Some of the patients with the greatest change would, in certain circumstances, be interpreted as masseteric muscle spasm potentially heralding MH. This could account for the large number of patients referred for MH screening who are shown to have normal muscle. It is also quite likely that a proportion of these may release so much skeletal muscle myoglobin as to exhibit overt myoglobinuria, increased serum CK concentration and hyperkalaemia [8]. With these signs, it is not surprising that anaesthetists interpret them as heralding MH—yet the patient can be differentiated from the true MH reactor by

demonstrating absence of hypermetabolism by measurement of blood-gas tensions and production of carbon dioxide, in addition to clinical monitoring of heart rate and body core temperature.

When patients are referred for MH screening following suxamethonium-induced masseteric spasm, it is unusual for the referring anaesthetist to comment on how long the abnormality lasted. This information might be important in distinguishing between normal subjects and those with muscle disease of MH. It is tempting to suggest that the longer the spasm lasts, the more likely it is for the patient to have abnormal muscle. Arbitrary limits have already been suggested [9], although we believe the information must be collected prospectively to make possible an answer to this important question.

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EFFECTS OF URAPIDIL, KETANSERIN AND SODIUM NITROPRUSSIDE ON VENOUS ADMIXTURE AND ARTERIAL OXYGENATION FOLLOWING CORONARY ARTERY BYPASS GRAFTING

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SUMMARY

Thirty patients who developed arterial hypertension following coronary artery bypass grafting, despite sedation, were treated randomly with sodium nitroprusside (SNP), ketanserin or urapidil. All drugs significantly decreased arterial pressure. Two patients were withdrawn because hypertension failed to respond to ketanserin. Significant tachycardia was noted only in the SNP group. An increase in $\dot{Q}$ and significant decreases in systemic and pulmonary vascular resistances were seen in all groups. Following administration of SNP, $(\text{PaO}_2 - \text{PaO}_{2s})$ and $\dot{Q}_s/\dot{Q}_t$ increased significantly, whereas PaO_2 decreased significantly. Three patients were withdrawn from the SNP group because $\dot{Q}_s/\dot{Q}_t$ was $> 30\%$. $(\text{PaO}_2 - \text{PaO}_{2s})$ and $\dot{Q}_s/\dot{Q}_t$ showed no significant changes following the administration of ketanserin or urapidil. These drugs may have advantages over SNP in the management of hypertension following coronary artery bypass surgery.

KEY WORDS

Complications: venous admixture. Pharmacology: sodium nitroprusside, ketanserin, urapidil. Surgery: coronary artery, postoperative hypertension.

A reduction in functional residual capacity (FRC) and an increase in lung water are observed commonly after extracorporeal circulation [1, 2]. This may lead to an increase in pulmonary shunt fraction, resulting in impairment of arterial oxygenation. The administration of antihypertensive drugs such as sodium nitroprusside (SNP), nitroglycerin, calcium channel blockers and other vasodilating drugs administered to

control arterial hypertension in the immediate postoperative period may further influence venous admixture ($\dot{Q}_s/\dot{Q}_t$) and arterial oxygenation [3-5]. This study was undertaken to determine the influence of urapidil (postsynaptic α_1 -adrenoceptor blocker with additional α_2 -adrenoceptor block, agonist of cerebral 5-HT_{1A} receptors in the brain [6-9]), ketanserin (selective 5-HT₂ receptor antagonist with additional α_1 -blocking effects [10-12]) and SNP on venous admixture and arterial oxygenation following coronary artery bypass grafting (CABG).

PATIENTS AND METHODS

The study was approved by the Ethics Committee and informed consent was obtained from all patients. Following CABG, 30 patients requiring control of postoperative arterial hypertension were allocated randomly to treatment with urapidil, ketanserin or sodium nitroprusside.

Before surgery, all patients had received β -blockers, calcium channel blockers and long acting nitrates. All patients were premedicated with lorazepam 1-2 mg 30 min before induction of anaesthesia with etomidate, sufentanil and pancuronium. Additional doses of midazolam, sufentanil and pancuronium were administered for maintenance of anaesthesia. Lidoflazine 1 mg kg⁻¹, a calcium channel blocker, was given

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for myocardial protection before extracorporeal circulation [13]. The lungs were ventilated with a mixture of air and oxygen ($F_{I_{O_2}}$ 0.5).

Arterial hypertension (systolic arterial pressure > 155 mm Hg, or 30 mm Hg greater than pre-operative values (average of three measurements)) recorded immediately after admission to the intensive care unit (ICU) was the indication for admission to the study. Patients were excluded if surgical blood loss was > 100 ml h⁻¹, left ventricular function was impaired (ejection fraction < 0.5, LVEDP > 12 mm Hg, ventricular dyskinesia present, cardiac index < 2.5 litre min⁻¹ m⁻²) or revascularization was incomplete. Inotropic support comprised less than 5 µg kg⁻¹ min⁻¹ of dopamine. Patients with pulmonary, renal or hepatic dysfunction were excluded.

Routine haemodynamic variables (ECG, systolic (SAP) and diastolic (DAP) arterial pressures, central venous pressure (CVP), systolic (PAS) and diastolic (PAD) pulmonary artery pressures) were monitored continuously. Pulmonary capillary wedge pressure (PCWP) was determined intermittently before administration of the test drug and 5, 60, 180, 420 and 720 min after the beginning of its administration. At each point, cardiac output ($\dot{Q}$) was measured by the thermodilution technique using cold isotonic saline. For each determination of $\dot{Q}$, three measurements were obtained and averaged.

After admission of the patient to the ICU, the lungs were ventilated mechanically: $F_{I_{O_2}}$ 0.5, PEEP + 5 cm H₂O. $F_{I_{O_2}}$ was maintained at this value for 30 min; subsequently, it was adjusted to

ensure normoxia, but was always > 0.3. Duplicate samples of arterial and mixed venous blood were obtained simultaneously before administration of the drug and 5, 60, 180, 420 and 720 min after administration. Arterial and mixed venous blood-gas tensions were measured in duplicate (ABL 4 Acid Base Laboratory) by the same individual on each occasion and averaged. Samples differing by > 1.3 kPa ($P_{a_{O_2}}$) were discarded and new samples obtained. $\dot{Q}_s/\dot{Q}_t$ was calculated from a standard formula [14]. Cardiac index (CI), systemic (SVRI) and pulmonary (PVRI) vascular resistance indexes and alveolar-arterial oxygen partial pressure difference ($P_{A_{O_2}} - P_{a_{O_2}}$) were calculated using standard formulae [15].

After operation all patients received, over 24 h, 800 ml m⁻² of a solution of glucose and balanced electrolytes. Blood and plasma were given according to the measured blood loss of each patient. All patients were sedated with fentanyl (single bolus) 3 µg kg⁻¹ i.v., piritramide 0.3 mg kg⁻¹/4 h i.m. and midazolam 0.1 mg kg⁻¹ h⁻¹ (maximum) i.v. Patients becoming hypertensive received, by random allocation, SNP 0.5–2 µg kg⁻¹ min⁻¹,

TABLE I. Patient characteristics (mean (SEM))

	Urapidil	SNP	Ketanserin
Age (yr)	61 (1.86)	62.2 (1.33)	61.5 (1.86)
Height (cm)	175.3 (2.1)	172 (2.5)	173.1 (2.9)
Weight (kg)	81.5 (5.2)	75.1 (3.7)	77.8 (4.2)
BSA (m ²)	1.94 (0.03)	1.87 (0.04)	1.89 (0.05)
Perioperative fluids (ml)	3500 (260)	3350 (210)	3600 (180)

TABLE II. Respiratory variables (mean (SEM)) in the treatment groups. Significant differences ($P < 0.05$): *within the group compared with control values; §between ketanserin and sodium nitroprusside; †between urapidil and sodium nitroprusside

	Control	5 min	60 min	180 min	420 min	720 min
Urapidil	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
$F_{I_{O_2}}$	0.5 (0)	0.5 (0)	0.47 (0.02)	0.48 (0.01)	0.45 (0.02)*	0.44 (0.02)*
$P_{a_{O_2}}$ (kPa)	23.61 (1.50)	21.38 (1.51)	19.61 (0.69)	19.81 (1.19)	19.32 (1.09)	19.19 (0.77)
$\dot{Q}_s/\dot{Q}_t$ (%)	8.52 (1.82)	10.58 (2.13)	11.0 (1.45)	10.58 (1.44)	10.25 (1.20)	10.1 (0.86)
($P_{A_{O_2}} - P_{a_{O_2}}$) (kPa)	22.86 (2.22)	23.45 (2.57)	21.89 (1.77)	21.44 (1.77)	20.54 (1.91)	18.74 (1.51)
Ketanserin	(n = 10)	(n = 10)	(n = 10)	(n = 8)	(n = 8)	(n = 8)
$F_{I_{O_2}}$	0.5 (0)	0.5 (0)	0.47 (0.02)	0.48 (0.01)	0.45 (0.02)*	0.44 (0.02)*
$P_{a_{O_2}}$ (kPa)	20.16 (1.61)	18.79 (1.61)	18.78 (1.48)	19.29 (0.66)	17.37 (0.97)	17.97 (0.74)
$\dot{Q}_s/\dot{Q}_t$ (%)	10.41 (1.33)	11.85 (1.49)	11.69 (1.57)	10.54 (0.74)	12.48 (0.91)	10.73 (0.82)
($P_{A_{O_2}} - P_{a_{O_2}}$) (kPa)	22.05 (1.92)	22.88 (2.06)	21.70 (1.14)	21.71 (1.14)	20.90 (1.19)	18.48 (1.71)
SNP	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 7)	(n = 7)
$F_{I_{O_2}}$	0.5 (0)	0.5 (0)	0.52 (0.015)†	0.51 (0.011)†	0.46 (0.019)	0.46 (0.019)
$P_{a_{O_2}}$ (kPa)	21.67 (1.36)	14.50 (1.42)*§†	15.76 (1.83)*	15.07 (1.77)*	16.94 (1.22)	16.62 (1.17)
$\dot{Q}_s/\dot{Q}_t$ (%)	10.26 (1.29)	19.02 (3.25)*§†	19.23 (2.61)*§†	19.71 (2.35)*§†	14.37 (1.18)	15.03 (0.88)
($P_{A_{O_2}} - P_{a_{O_2}}$) (kPa)	23.46 (2.75)	25.23 (3.04)	15.76 (1.83)*§†	15.07 (1.77)*§†	16.94 (1.22)	16.62 (1.17)

TABLE III. Haemodynamic variables (mean (SEM) in the treatment groups. Significant differences ($P < 0.05$): * within the group compared with control values; † between urapidil and sodium nitroprusside

	Control	5 min	60 min	120 min	180 min	420 min	720 min
Urapidil							
HR (beat min ⁻¹)	(n = 10) 92.6 (3.61)	(n = 10) 92.6 (4.11)	(n = 10) 89.8 (4.42)	(n = 10) 85.6 (3.17)	(n = 10) 84.2 (3.17)	(n = 10) 81.5 (2.87)	(n = 10) 80 (2.21)
SAP (mm Hg)	186 (4.89)	132.7 (3.28)*	129.8 (3.83)*	131.4 (3.11)*	131.1 (2.77)*	121.6 (3.905)*	119.1 (3.08)*
PAS (mm Hg)	29.2 (2.18)	24.1 (1.66)*	22.5 (1.68)*	28.5 (2.05)	26.7 (2.19)	27.1 (2.22)	26.2 (1.65)
PCWP (mm Hg)	8.7 (0.98)	6.9 (0.74)	6.4 (0.83)	8.8 (0.73)	8.5 (0.83)	8.9 (0.36)	9.1 (0.79)
Q̇ (litre min ⁻¹ m ²)	3.4 (0.26)	4.16 (0.32)*	4.23 (0.43)*	4.15 (0.44)*	4.16 (0.42)*	3.7 (0.24)	3.7 (0.21)
TPRI (dyn s cm ⁻⁵ m ²)	2726.5 (275.60)	1510.6 (141.40)*	1414.4 (163.50)*	1498.1 (134.50)*	1488.6 (159.60)*	1407.9 (122.90)*	1479 (102.80)*
PVRI (dyn s cm ⁻⁵ m ²)	241.8 (28.91)	184.1 (23.30)*	174.2 (21.51)*	212.4 (27.26)	200.6 (27.02)	186.7 (25.57)*	143.9 (20.69)*
Ketanserin							
HR (beat min ⁻¹)	(n = 10) 89.7 (2.91)	(n = 10) 97.3 (4.23)	(n = 10) 93.2 (5.50)	(n = 9) 95.3 (4.66)	(n = 8) 94.25 (4.28)	(n = 8) 90.13 (3.71)	(n = 8) 91.5 (4.58)
SAP (mm Hg)	184 (6.09)	140.7 (5.06)*	143.4 (7.37)*	146.9 (9.10)*	129.9 (5.02)*	129.6 (5.87)	123 (3.97)*
PAS (mm Hg)	27.30 (2.49)	22.60 (1.54)*	24.40 (2.04)	25.30 (1.19)	24.63 (1.33)	25.88 (1.21)	24.75 (1.48)
PCWP (mm Hg)	9.70 (1.31)	7.60 (1.00)	8.20 (1.17)	9.30 (1.18)	8.25 (0.60)	9.37 (0.89)	9.75 (0.75)
Q̇ (litre min ⁻¹ m ²)	3.34 (0.15)	3.59 (0.23)	3.67 (0.21)	3.54 (0.16)	3.46 (0.15)	3.57 (0.21)	3.43 (0.13)
TPRI (dyn s cm ⁻⁵ m ²)	2508 (174.20)	1781 (133.00)*	1724 (147.00)*	1788 (143.60)*	2019 (374.70)	1569 (81.70)*	1555 (85.30)*
PVRI (dyn s cm ⁻⁵ m ²)	250.9 (27.95)	197.0 (19.92)*	221.80 (26.02)	205.6 (15.19)	221.35 (14.80)	223.7 (20.62)	198.6 (23.39)*
SNP							
HR (beat min ⁻¹)	(n = 10) 91 (2.81)	(n = 10) 104.1 (3.49)*†	(n = 10) 94.89 (3.63)	(n = 10) 86.33 (2.20)	(n = 10) 87.63 (2.29)	(n = 7) 82.71 (3.56)	(n = 7) 82.86 (3.28)
SAP (mm Hg)	180.5 (2.49)	142.6 (2.90)*	131.6 (3.05)*	133.8 (4.52)*	134.9 (2.69)*	130.5 (5.11)*	133.5 (5.16)*
PAS (mm Hg)	27.6 (2.06)	25.2 (2.36)	26.33 (2.04)	25.11 (1.62)	26 (2.03)	25.17 (1.27)	28 (3.02)
PCWP (mm Hg)	10.7 (1.37)	7.2 (1.19)	8.0 (1.00)	8.22 (0.77)	7.75 (0.79)	7.71 (0.67)	7.72 (0.98)
Q̇ (litre min ⁻¹ m ²)	3.46 (0.26)	3.67 (0.32)	3.81 (0.17)	3.66 (0.21)	3.57 (0.22)	3.58 (0.22)	3.70 (0.26)
TPRI (dyn s cm ⁻⁵ m ²)	2281.1 (244.10)	1595.6 (178.30)*	1440.8 (73.80)*	1571.2 (99.10)*	1643.7 (130.20)*	1642.0 (135.50)*	1578.0 (89.02)*
PVRI (dyn s cm ⁻⁵ m ²)	223.0 (25.64)	219.0 (24.80)	206.1 (25.79)	219.3 (17.78)	253.6 (36.86)	212.8 (21.36)	240.4 (24.13)†

urapidil (initial bolus of 25 mg, followed by an infusion of 30–90 mg h⁻¹) or ketanserin (initial bolus of 10 mg over 60 s, second bolus of 10 mg if necessary and an infusion of 1–5 µg kg⁻¹ min⁻¹).

Data are presented as mean (SEM). Statistical analyses were performed using the Friedmann and Wilcoxon test (including Bonferroni correction) for intragroup comparisons and the Kruskal–Wallis and Mann–Whitney rank sum tests for intergroup comparisons. Significant differences were accepted when $P \leq 0.05$.

RESULTS

Thirty patients were studied (10 in each group). Two patients had to be withdrawn from the ketanserin group (one patient after 1 h, the second after 2 h), because of persistent hypertension. Three patients were withdrawn from the SNP group (after 3 h) because of an increase in $\dot{Q}_s/\dot{Q}_t$ to > 30% and an intolerable decrease in P_{aO_2} , despite an increase in Fi_{O_2} .

There were no statistically significant differences between the groups in age, sex, weight or volume of colloids and crystalloids administered (table I).

The maximum decrease in P_{aO_2} in the urapidil and ketanserin groups was 1.43 (0.38) kPa and 1.37 (0.32) kPa, respectively (ns). In the SNP group, P_{aO_2} decreased significantly by 7.17 (0.83) kPa compared with control values and the other groups. ($P_{aO_2} - P_{aO_2}$) decreased after the administration of urapidil and ketanserin, but increased significantly in SNP-treated patients compared with control values and the other groups. $\dot{Q}_s/\dot{Q}_t$ increased significantly from 10.26 (1.29)% to 19.02 (3.25)% after the administration of SNP and also with respect to the other groups (table II).

In all groups there were significant decreases in SAP: maximum change in the SNP group was 60.2 (5.66) mm Hg, in the urapidil group 66.9 (6.3) mm Hg and in the ketanserin group 61.0 (6.11) mm Hg. A significant increase in heart rate of 13.1 (1.93) beat min⁻¹ was seen in the SNP group compared with control and the urapidil group. PAS, PAP and PCWP decreased during administration of all the drugs. Although CVP decreased in all groups, none of the changes was significant. $\dot{Q}$ increased significantly in the SNP and urapidil groups. SVRI and PVRI decreased significantly in all groups (table III).

DISCUSSION

Early postoperative hypertension after CABG is common and has an incidence of 30–60% [11, 16, 17]. In this study, it was controlled adequately by urapidil and SNP. However, in the ketanserin group, two patients had to be withdrawn from the study as treatment failures.

A significant increase in heart rate was observed after administration of SNP. Tachycardia following CABG may lead to an increase in myocardial oxygen consumption and result in myocardial ischaemia. Urapidil and ketanserin in this setting may be superior, as no significant increases in heart rate were seen in either of these groups. Prevention of tachycardia by urapidil may be a result of central inhibition of sympathetic activity by stimulation of 5-HT_{1A} receptors in the medulla oblongata [7]. Ketanserin is thought to inhibit the sympathetic outflow of catecholamines and to lead to an inhibition of central α_1 -adrenergic receptors [12, 17].

An increased $\dot{Q}_s/\dot{Q}_t$ with subsequent deterioration in systemic oxygenation was seen, in common with previous studies [1, 2]. Hypoxic pulmonary vasoconstriction, described first in 1946 by von Euler and Liljestrand [18], is an important mechanism by which blood flow is diverted away from atelectatic or hypoxic regions of the lung. Many vasodilating drugs, including SNP, inhibit hypoxic pulmonary vasoconstriction, increasing $\dot{Q}_s/\dot{Q}_t$ and decreasing P_{aO_2} [2–5, 17, 19]. However, after administration of ketanserin and urapidil no increase in $\dot{Q}_s/\dot{Q}_t$ or decrease in P_{aO_2} was seen in the present study, suggesting that these drugs did not inhibit hypoxic pulmonary vasoconstriction. This has been shown for ketanserin in patients with ARDS. The authors concluded that ketanserin might be a less potent pulmonary vasodilator than SNP [20].

Urapidil and ketanserin appear to have advantages compared with SNP in the treatment of hypertension following CABG with respect to oxygenation and heart rate. However, 20% of the patients receiving ketanserin were withdrawn as treatment failures.

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INFLUENCE OF HYPOTENSION AND HYPOTENSIVE TECHNIQUE ON THE AREA OF PROFOUND REDUCTION IN CEREBRAL BLOOD FLOW DURING FOCAL CEREBRAL ISCHAEMIA IN THE RAT

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SUMMARY

We have studied the effect of induced hypotension on reduction in regional cerebral blood flow (CBF) during middle cerebral artery occlusion (MCAO). Rats were anaesthetized with 2% isoflurane. MCAO was performed during four conditions: normotension (mean arterial pressure (MAP) 107 (SD 15) mm Hg); hypovolaemic hypotension (blood withdrawn to reduce MAP to 43 (2) mm Hg); nitroprusside (SNP) hypotension (MAP reduced to 45 (3) mm Hg); isoflurane hypotension (MAP reduced to 44 (3) mm Hg with 3.5 (0.48) % isoflurane). Hypotension was established before MCAO and was maintained for 10 min, at which time the dimension of the brain areas with zero CBF was determined autoradiographically. All hypotensive regimens were associated with significantly larger areas of extreme CBF reduction. In a coronal section at the centre of the MCA distribution, the area with zero CBF (expressed as a percentage of the area of the entire coronal section) was: normotension 4.7 (4.5) %; hypovolaemic hypotension 10.1 (2.8) %; nitroprusside hypotension 13.5 (2.0) %; and isoflurane hypotension 11.8 (3.9) %. There were no differences between the three hypotensive regimens. The data indicate that, when focal cerebral ischaemia occurs during hypotension (MAP 45 mm Hg) induced by any of the three regimens evaluated, extreme CBF reduction occurs over larger areas than are observed during normotension. These data confirm the importance of arterial pressure as a determinant of collateral flow during focal cerebral ischaemia.

KEY WORDS

Anaesthetic technique: hypotension, induced. Brain: blood flow, focal ischaemia.

Induced hypotension is used both electively and in urgent circumstances during the surgical management of intracranial aneurysms. Focal cerebral ischaemia may occur during these operations, for several reasons. Vasospasm of varying degree may be present, especially when clipping is performed in the acute phase following subarachnoid haemorrhage. Inadvertent occlusion of a cerebral artery (e.g., the middle cerebral artery) or of its branches (e.g., the lenticulostriates) may occur during temporary placement of aneurysm clips, and vessel occlusion may occur also as a result of clipping an aneurysm under the circumstances of reduced visibility that arise following rupture of an aneurysm. Elective "trapping" of an aneurysm may also cause temporary focal cerebral ischaemia.

Because of the risk of focal cerebral ischaemia during aneurysm surgery, it is important that the effect of anaesthetic agents and techniques on

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neuronal survival is understood. The present study has examined the dimension of the area of extreme cerebral blood flow (CBF) reduction occurring with three methods of induced hypotension following occlusion of the middle cerebral artery in the rat.

METHODS

The study was approved by the Animal Use Subcommittee of the Veterans' Administration Medical Center, La Jolla, California. Male Sprague-Dawley rats (wt 350–450 g) were fasted for 14 h before the study, but were allowed free access to water. Anaesthesia was induced with the animal in a plexiglass box, using 4% isoflurane in oxygen. The trachea was intubated and the lungs were ventilated mechanically with an inspired gas mixture of 2% isoflurane and 40% oxygen in nitrogen. Ventilation was adjusted to maintain normocapnia. Rectal temperature was maintained at 37 °C. Catheters (PE-50) were placed in both femoral arteries and veins. Mean arterial pressure (MAP), the electrocardiogram and rectal temperature were monitored continuously. Arterial blood-gas tensions and haematocrit were measured intermittently. A left subtemporal craniectomy was performed according to the method of Tamura and colleagues [1]. The subsequent middle cerebral artery occlusion was performed according to the method of Bederson and colleagues [2].

Following completion of the craniectomy, the rats were assigned randomly to one of four experimental groups: normotensive control; hypovolaemic hypotension; nitroprusside hypotension; isoflurane hypotension. In the control group, the inspired isoflurane concentration was maintained at 2.0%. In the other three groups, hypotension was induced 15 min after completion of the craniectomy. MAP was reduced slowly over a period of 15–20 min by gradual withdrawal of blood via an arterial line, a gradual increase in inspired concentration of isoflurane, or a gradual increase in rate of infusion of 0.5% sodium nitroprusside. When mean arterial pressure (MAP) had been decreased to 50–55 mm Hg, a small incision was made in the dura over the middle cerebral artery (MCA) in the vicinity of the olfactory tract. The MCA was occluded in all four groups, using micro-bipolar forceps under saline irrigation. The occlusion extended from a point just proximal to the olfactory tract, to the

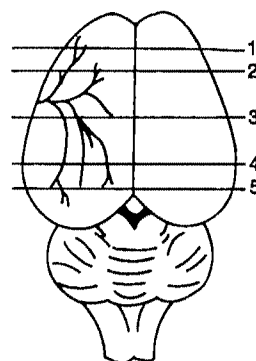


FIG. 1. Dorsal view of the rat brain showing the orientation of the five coronal sections in which the area of severe ischaemia was determined. See text for additional information. The distribution of the cortical portion of the left MCA has been redrawn after Brint and colleagues [3].

inferior cerebral vein [2]. During the final exposure and occlusion of the MCA, arterial pressure was decreased further, to 45 mm Hg. Arterial pressure was held stable at this value for 10 min after MCA occlusion (MCAO), at which time non-quantitative determination of CBF was performed.

^{14}C -Iodo-antipyrine $100 \mu\text{Ci kg}^{-1}$ was infused over a period of 46 s. The animal was decapitated at $t = 45$ s and the brain was removed rapidly and placed immediately in 2-methyl-isobutane in a freon bath. The brains were subsequently cut in a cryostat at -13°C . Coronal sections ($20 \mu\text{m}$) were exposed on Kodak OM-1 film for 21 days. Five standard coronal sections (designated 1–5) spanning the anterior–posterior extent of the zone of ischaemia were analysed (fig. 1). Section 2 was located at the anterior midline extent of the corpus callosum; section 4 was located at the posterior midline extent of the corpus callosum; section 1 was 1.8 mm anterior to section 2; section 3 was midway between sections 2 and 4; section 5 was 1.8 mm posterior to section 4. Sections 1–5 correspond to Plates 5, 11, 22, 34 and 40, respectively, in *Maps and Guides to Microdissection of the Rat Brain* by Palkovits and Brownstein [4].

A Drexel DUMAS image processing system (Drexel University Image Processing Center, Philadelphia, PA) was used to identify the regions of each brain section with an optical density equivalent to background—that is, those areas in which cerebral blood flow was zero and in which there had been no accumulation of isotope. The area of zero flow was expressed as a percentage of

TABLE I. *Physiological variables (mean (SD)) at the time of CBF determination 10 min after MCAO. ***P < 0.0001 vs control; **P < 0.01 vs control and isoflurane*

	Control	Hypovolaemia	Isoflurane	Nitroprusside	ANOVA
MAP (mm Hg)	107 (15)	43 (2)***	44 (3)***	45 (3)***	$P < 0.0001$
P_{aCO_2} (kPa)	5.0 (0.2)	4.9 (0.1)	5.0 (0.2)	5.2 (0.4)	ns
P_{aO_2} (kPa)	16.9 (1.3)	16.9 (2.0)	16.0 (2.9)	15.0 (2.2)	ns
pH	7.40 (0.02)	7.39 (0.01)	7.39 (0.04)	7.38 (0.04)	ns
Packed cell volume (%)	46 (1)	41 (2)**	45 (1)	44 (2)	$P < 0.001$

TABLE II. *Percentage (SD) of each coronal section with zero blood flow 10 min after MCAO. *P < 0.05 vs control; †P < 0.05 vs hypovolaemia*

Section	Control	Hypovolaemia	Isoflurane	Nitroprusside	ANOVA
1	1.0 (1.8)	3.5 (3.6)	7.6 (5.6)*	9.7 (5.4)*†	$P < 0.01$
2	2.9 (4.2)	9.0 (4.4)*	10.6 (6.2)*	14.8 (3.9)*	$P < 0.01$
3	4.7 (4.5)	10.1 (2.8)*	11.8 (3.9)*	13.5 (2.0)*	$P < 0.01$
4	1.0 (1.4)	3.9 (3.2)	6.9 (3.8)*	7.4 (3.7)*	$P < 0.01$
5	0.2 (0.2)	0.7 (0.8)	3.2 (3.2)*	2.7 (2.3)	$P < 0.01$

the cross-sectional area of the entire coronal section.

Data were analysed using one-way analysis of variance. Where differences were identified, multiple pairwise comparisons were performed using the Newman-Keuls multiple range test [5].

RESULTS

Of the 31 animals studied, three (one control and two nitroprusside) were excluded for technical reasons. The remaining 28 animals were allocated evenly to the four groups. At the time of determination of CBF (10 min after MCAO) there were no differences between the groups in terms of P_{aCO_2} , P_{aO_2} and pH (table I). MAP was significantly ($P < 0.0001$) greater in the control group (107 (SD 15) mm Hg) than in the three hypotensive groups (hypovolaemia 43 (2) mm Hg; isoflurane 44 (3) mm Hg; nitroprusside 45 (3) mm Hg); differences between the three hypotensive groups were not significant. The inspired isoflurane concentration was significantly greater in the isoflurane hypotension group (3.5 (0.48)%) than in the other three groups.

MCAO resulted in an autoradiographically obvious area of ipsilateral flow reduction that included lateral and dorsolateral cortex and the corpus striatum. Each of the three hypotensive regimens was associated with a significantly larger area of ischaemia than was seen in the normo-

tensive control group (table II). The differences between the normotensive control group and the hypotensive groups were significant in five of the five sections for isoflurane, in four of the five sections for nitroprusside, and in two of the five sections for hypovolaemia. The increases in the area of ischaemia caused by hypotension were substantial. For the middle section (section 3) the ischaemic areas (expressed as a percentage of the area of the entire coronal section) were: control 4.7 (4.5)%; hypovolaemia, 10.1 (2.8)%; isoflurane, 11.8 (3.9)%; nitroprusside, 13.5 (2.0)%. The only significant difference (Newman-Keuls multiple range test) among the three hypotensive regimens occurred in section 1, in which the ischaemic area was larger ($P < 0.05$) in the nitroprusside group than in the hypovolaemia group.

DISCUSSION

This investigation examined the area of profound CBF reduction present 10 min after MCAO in the rat. One limitation of the results is that they provide information on the status of the cerebral circulation at only one moment following MCAO. Ten minutes was chosen because it is within the range of intervals that occur when temporary vascular occlusions take place during operation. A second limitation is that CBF at one moment is not necessarily a predictor of neuronal outcome. Therefore, it is not certain that the substantial CBF differences we observed would have resulted

in differences in neuronal survival if reperfusion had occurred. However, our method measured the area in which CBF was essentially zero, and it is established that CBF reduction of this magnitude results very quickly in neuronal death [6]. Thus our data support the view that induced hypotension with all three of the regimens studied would have resulted in greater neuronal loss than would have occurred during normotensive MCAO.

A mean arterial pressure of approximately 45 mm Hg was chosen because it is similar to the values utilized in precarious clinical situations. An MAP of 45 mm Hg is slightly less than the reported lower limit of normal autoregulation (approximately 50 mm Hg) for a variety of species ranging from rats [7] to primates [8]. However, it seems unlikely that the increase in the ischaemic area seen with hypotension was entirely the result of this small reduction of MAP beyond the autoregulatory threshold. It is probable that the vasculature within and at the periphery of the area of substantial CBF reduction is pressure passive [9] and that the development of collateral flow to the ischaemic area is dependent upon perfusion pressure. The increased extent of severe ischaemia seen with all three hypotensive regimens is consistent with the concept that the degree of arterial pressure reduction is a more important determinant of CBF distribution than the effect of the hypotensive agent on normal cerebral vessels.

By the multiple comparison method (Newman-Keuls test) used in the initial data analysis, the only significant difference among the three hypotensive groups occurred in section 1, in which the ischaemic area was larger ($P < 0.05$) in the nitroprusside group than in the hypovolaemia group. However, inspection of the data in table II suggested a trend toward additional differences. We therefore performed *post hoc* comparisons between the three hypotensive groups using Student's *t* test for unpaired data (without corrections for multiple comparisons). This approach increases the power of the statistical analysis, but adds to the risk of a false positive statistical error. By this method there were no differences for the comparisons of hypovolaemia *vs* isoflurane and isoflurane *vs* nitroprusside. However, the comparison of hypovolaemia *vs* nitroprusside revealed significantly larger areas of ischaemia in the nitroprusside group in sections 1, 2 and 3. Before the study was performed, this apparent difference had not been anticipated. In

previous investigations performed in normal animals comparing hypotension induced by nitroprusside and by haemorrhage, nitroprusside was associated with either greater or equivalent preservation of CBF [10–13]. The most likely explanation is that haemorrhagic hypotension causes cerebral vasoconstriction because of high circulating concentrations of catecholamine, activation of sympathetic innervation of the cerebral vasculature, or both [4, 5]. This theory may be consistent with the present results. It is possible that, with focal ischaemia (present study) rather than global ischaemia, catecholamine-mediated vasoconstriction may result in shunting (a "Robin Hood steal") of blood away from non-ischaemic regions to the jeopardized areas (in which there is vasoparalysis). Both isoflurane and sodium nitroprusside are known cerebral vasodilators [16–19] and it follows that, in the presence of focal ischaemia, vasodilatation of normal vessels may result in the opposite phenomenon, with shunting ("steal") of blood away from ischaemic brain to adjacent normal tissue.

The data analysis indicates that the sizes of the areas of profound ischaemia were similar for nitroprusside and isoflurane. However, it is probable that different cerebral metabolic circumstances prevailed during the two hypotensive regimens. Isoflurane caused a substantial reduction in cerebral metabolic rate (CMR) [16]; thus CMR was probably lower in the isoflurane group than in the nitroprusside group. Accordingly, equivalent degrees of reduction in CBF observed in these two groups may represent different degrees of physiological impairment, with the isoflurane group relatively "protected" as a result of metabolic suppression [20, 21].

The methods used to compare the three hypotensive regimens measured only the areas of severe reduction in flow. Neuronal death would be likely to ensue rapidly in these areas. The study did not examine the so-called ischaemic penumbra, in which the extent of reduction in CBF is such that neurones are impaired functionally, but potentially recoverable; the relative effect of the various regimens may be different in terms of the dimension of the penumbra.

In summary, the present results suggest that, when induced hypotension occurs in the presence of focal ischaemia, there may be a substantial increase in the area of severely ischaemic brain. In terms of the area of profound flow reduction

occurring after MCAO in the rat, there was little difference between hypotension accomplished with either deep isoflurane anaesthesia or sodium nitroprusside administered during light isoflurane anaesthesia. These data suggest that, in situations in which focal ischaemia is present or may occur, induced hypotension should be undertaken only after careful consideration of the risks and benefits.

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ASPIRATION PNEUMONITIS PROPHYLAXIS IN OBSTETRIC ANAESTHESIA: COMPARISON OF EFFERVESCENT CIMETIDINE-SODIUM CITRATE MIXTURE AND SODIUM CITRATE

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SUMMARY

One hundred and forty-seven patients undergoing elective or emergency Caesarean section under general anaesthesia were allocated randomly to three groups: group 1 ($n = 28$) received no premedication; group 2 ($n = 58$) received 0.3-molar sodium citrate 15 ml (sodium citrate 1.16 g); group 3 ($n = 61$) received effervescent cimetidine-sodium citrate combination (cimetidine 400 mg with sodium citrate 0.9 g) after entering the operating room. Gastric pH was measured at tracheal intubation (pH1) and extubation (pH2). Mean pH1 and mean pH2 values in group 1 were, respectively, 2.25 (SD 1.35) and 2.83 (1.64). Mean pH1 and pH2 values in group 2 were, respectively, 4.38 (1.44) and 4.57 (1.51). In group 3 mean pH1 and pH2 values were, respectively, 5.07 (1.13) and 5.37 (1.30). Percentages of patients with pH1 ≤ 2.5 in groups 1, 2 and 3 were, respectively, 75, 13.8 and 1.6. Percentages of patients with pH2 ≤ 2.5 in groups 1, 2 and 3 were 50, 10.3 and 1.6, respectively.

KEY WORDS

Anaesthesia: obstetric. Complications: aspiration, prophylaxis. Gastrointestinal tract: antacids, cimetidine.

after labour has begun [2, 3]. Obstetric patients are particularly at risk because of the potentially large gastric residue with pH less than 2.5. An aqueous antacid, sodium citrate, and H_2 -receptor antagonists (cimetidine and ranitidine) have been studied as means of increasing gastric pH to more than 2.5. Sodium citrate may be used in emergency surgery because of its immediate onset of antacid action [4, 5], but it exhibits wide variations in efficacy and duration of action [6-12]. Cimetidine and ranitidine increase gastric pH by inhibiting gastric acid production for 4-8 h [13], but the delay in onset of action makes these compounds unsuitable for aspiration pneumonitis prophylaxis in emergency obstetric anaesthesia unless a multiple dose regimen is started when labour begins.

A new formulation of cimetidine (Tagamet 800 effervescent, Smith Kline and French Laboratories) has been developed recently. This combines cimetidine 800 mg with sodium citrate 1.8 g as effervescent excipient. It provides an immedi-

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The aspiration of gastric contents into the lungs (first studied by Mendelson [1]) remains the major cause of anaesthetic death among obstetric patients; it occurs mostly in emergency situations

ately available acid neutralizing capacity of hydrochloric acid 14.8 mmol per tablet at pH 3.5 (USP method).

The purpose of the present study was to evaluate in patients undergoing elective or emergency Caesarean section the efficacy of this new compound in increasing gastric pH and to compare it with that of sodium citrate 0.3 mol litre⁻¹.

PATIENTS AND METHODS

This study was undertaken in five hospitals. It was approved by the local Ethics Committees, and all patients gave informed consent. We randomly allocated 147 patients (ASA I or II) to three groups: group 1, control ($n = 28$) received no premedication; group 2 ($n = 58$) received 0.3-molar sodium citrate 15 ml (sodium citrate 1.16 g); and group 3 ($n = 61$) received half of a tablet of Tagamet 800 effervescent (cimetidine 400 mg with sodium citrate 0.9 g) in 15 ml of water after entering the operating room.

Patients undergoing elective Caesarean section were fasted for a minimum of 8 h. Patients for emergency Caesarean section were fasted after arrival in hospital and in established labour. General anaesthesia was induced with thiopentone 5 mg kg⁻¹ and suxamethonium 1.5 mg kg⁻¹ i.v. After tracheal intubation was performed, anaesthesia was maintained with 50% nitrous oxide in oxygen (with 0.5% halothane if necessary) and vecuronium 70 µg kg⁻¹ until delivery of the baby, when fentanyl 200–500 µg was administered. Oxytocin was administered i.v. to decrease uterine bleeding. After tracheal intubation, a 16-French gauge Salem orogastric tube was passed and a 10-ml sample of gastric content aspirated. Immediately before extubation, the remaining gastric fluid was removed. pH of each sample was

measured using a Beckman 71 pH meter. First and second sampling times were recorded for each patient.

The study of group 1 was discontinued after 28 patients had been studied, because a large number of patients was found with gastric pH less than 2.5. There were three dry samplings in each group.

We compared the patient groups for age, weight, interval between antacid premedication and first and second samplings, percentage of emergency cases, and gastric pH. Numerical data were analysed using multivariate analysis of variance, Student's *t* test or Wilcoxon's rank test as appropriate. Ordinal data were compared using Fisher's exact test or chi-squared test as appropriate. Spearman's rank correlation was used to examine the correlation between the values of pH at intubation and extubation and first and second sampling intervals in groups 2 and 3. We considered $P \leq 0.05$ significant.

RESULTS

Median values for first sampling interval were 19.6 min (range 10–55 min) in group 2, and 19.7 min (range 10–50 min) in group 3 (ns) (table I). Median values of second sampling interval were 58.5 min (range 40–110 min) in group 2, and 60.5 min (range 40–120 min) in group 3 (ns) (table I).

In group 1, mean values of pH at intubation (pH1) and extubation (pH2) were significantly less than ($P < 0.001$) in groups 2 and 3 (table II).

In group 1, percentages of patients with pH1, and pH2 ≤ 2.5 were significantly greater than in groups 2 and 3 (table II).

Mean pH1 and mean pH2 in group 3 were significantly greater and the percentage of patients

TABLE I. Patient characteristics (mean (SD), median (range) or number (percentage)). Group 1 = Control; group 2 = 0.3-molar sodium citrate 15 ml; group 3 = cimetidine 400 mg with sodium citrate 0.9 g. No significant differences

	Group 1 ($n = 28$)	Group 2 ($n = 58$)	Group 3 ($n = 61$)
Age (yr)	29.2 (6.2)	28.5 (5.7)	28.3 (5.1)
Weight (kg)	72 (13.9)	73 (14.1)	69.2 (13.8)
First sampling interval (min)		19.6 (10–55)	19.7 (10–50)
Second sampling interval (min)		58.5 (40–110)	60.5 (40–120)
Emergency Caesarean section	12 (42.8%)	26 (44.8%)	29 (47.5%)

TABLE II. pH values (mean (SD)) at intubation (pH1) and extubation (pH2), and number and percentages of patients with pH1 and pH2 less than 2.5 in groups 1 (control), 2 (0.3-molar sodium citrate 15 ml) and 3 (cimetidine 400 mg with sodium citrate 0.9 g). ***P < 0.001 compared with other groups at the time control was ended; †††P < 0.001 compared with group 3; **P < 0.01 compared with group 2; ††P < 0.01 compared with group 3; *P < 0.05 compared with group 3

	Group 1 (n = 28)	Group 2 (n = 58)	Group 3 (n = 61)
pH1	2.25 (1.35)***	4.38 (1.44)††	5.07 (1.13)
pH2	2.83 (1.64)***	4.57 (1.51)††	5.37 (1.30)
Patients with			
pH1 ≤ 2.5	21 (75%)***	8 (13.8%)*	1 (1.6%)
pH2 ≤ 2.5	14 (50%)†††**	6 (10.3%)	1 (1.6%)

TABLE III. Spearman's rank correlation coefficient (r) between pH and sampling intervals. T1 = Time between antacid prophylaxis and first sampling; T2 = Time between antacid prophylaxis and second sampling. Group 2 = 0.3-molar sodium citrate 15 ml; group 3 = cimetidine 400 mg with sodium citrate 0.9 g

	Group 2		Group 3	
	T1 (n = 58)	T2 (n = 55)	T1 (n = 61)	T2 (n = 58)
pH1	r = -0.260 P < 0.05		r = -0.249 ns	
pH2		r = 0.047 ns		r = 0.046 ns

with pH1 ≤ 2.5 was significantly smaller than in group 2 (table II). In group 3, only one patient of 61 had a pH ≤ 2.5 at intubation and extubation.

In groups 2 and 3, percentages of patients with a pH2 ≤ 2.5 were not significantly different, but in group 2, there were two dry second samplings in patients with pH1 ≤ 2.5.

There was a correlation between pH1 and first sampling interval only in group 2, with pH1 decreasing as first sampling interval increased. There was no correlation between pH2 and second sampling interval in groups 2 and 3 (table III).

DISCUSSION

This study has shown that the new effervescent cimetidine-sodium citrate combination administered 10-50 min before surgery was effective in increasing gastric pH at both tracheal intubation and extubation in patients undergoing planned or emergency Caesarean section. This study has also shown that this new compound was more effective than 0.3-molar sodium citrate 15 ml in increasing pH at intubation and extubation.

Although gastric volume is an important factor in the pulmonary damage caused by acid aspiration [14], we did not measure this variable because it is difficult to assess accurately and because volume may be less important than pH in causing lung damage [15].

Results of studies on sodium citrate have been conflicting: 0.3-molar sodium citrate 15 ml was found to be either effective [6-8] or ineffective [9] in increasing gastric pH to more than 2.5. Gastric pH values were shown to increase for a short [10] or long [11] interval with 0.3-molar sodium citrate 30 ml. Two studies [4, 5] using continuous *in vivo* measurements of intragastric pH in pregnant women at term have shown that sodium citrate neutralizes acid immediately, but the critical factor influencing its duration of action is the rate of gastric emptying. Therefore, analgesics which delay gastric emptying [16] prolong the efficiency of sodium citrate. Our data with sodium citrate confirm that this antacid was not always efficient in increasing gastric pH to more than 2.5.

The percentages of patients with pH ≤ 2.5 at intubation and extubation in group 2 were not significantly different, probably because during anaesthesia all patients were given analgesics after the birth of the baby, thereby prolonging the action of sodium citrate. In contrast, the effervescent cimetidine-sodium citrate combination increased gastric pH to more than 2.5 at intubation and extubation in 98.4% of patients. This finding is consistent with that of a preliminary study [17]. It is surprising that about the same amount of sodium citrate (1.16 g in group 2; 0.9 g in group 3) produced different results when given alone or in combination with cimetidine. This may be caused by onset of action of cimetidine at the first sampling time. Unpublished data [J.B. Fourtillan and colleagues] suggest that Tagamet 800 effer-

vescent produces therapeutic [18] cimetidine plasma concentrations (more than $0.5 \mu\text{g ml}^{-1}$ in healthy adults) in 15 min, whereas the same dose of cimetidine in a non-effervescent formulation produced lower plasma concentrations at this time.

In our study, the values of pH at extubation with the cimetidine-sodium citrate combination reflect the long duration of antacid action of this compound. This is in agreement with a study undertaken in healthy adults with Tagamet 200 effervescent, a combination of cimetidine 200 mg with sodium citrate 1.8 g [19].

In summary, the new effervescent cimetidine-sodium citrate formulation was effective in increasing gastric pH to more than 2.5 at intubation and extubation in obstetric patients undergoing elective or emergency surgery, and was more effective than 0.3-molar sodium citrate 15 ml.

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GAS EXCHANGE DURING ANAESTHESIA

G. HEDENSTIERNA

The lungs oxygenate blood less efficiently in the anaesthetized than the awake subject. Defective arterial oxygenation after pulmonary resection was reported as early as 1943 by Maier and Courmand [25], and in 1958 Campbell and co-workers [7] showed that anaesthesia was often associated with increased alveolar-arterial oxygen partial pressure difference. However, despite almost 50 years' awareness of impaired gas exchange during anaesthesia, the causes underlying this impairment have remained unclear until recently. This review considers the different mechanisms by which arterial oxygenation may be impaired.

Compliance and functional residual capacity (FRC)

In 1955, Nims and co-workers [29] found that the static compliance of the total respiratory system (lungs and chest wall) was reduced in the anaesthetized subject, and in succeeding studies lung compliance was shown to be lower in the anaesthetized than in awake subjects (for a review, see [9]). Bendixen and co-workers [1] reported continuously decreasing compliance during anaesthesia, accompanied by a similarly decreasing arterial partial pressure of oxygen (Pa_{O_2}). Following large inflations of the lungs, compliance and Pa_{O_2} increased. The authors considered that this indicated slow development of absorption atelectasis. However, other research groups were unable to confirm the findings of Bendixen's group [31, 41]; and atelectasis could not be seen by conventional chest x-ray. Atelectasis as a mechanism of impaired gas exchange was rejected, therefore.

In the same year as Bendixen and co-workers proposed the concept of atelectasis, Bergman [2]

published the first report on reduced functional residual capacity (FRC) during anaesthesia. Since then, several studies have shown a fairly consistent decrease in FRC during anaesthesia of approximately 20%, during either spontaneous ventilation or controlled ventilation using neuromuscular blocking drugs (for a review, see [35]).

With reduced FRC, a shift in the position of the rib-cage or diaphragm may be anticipated. Using cineradiography, Froese and Bryan [12] demonstrated cranial shift of the diaphragm during anaesthesia, with no further shift after production of muscle paralysis. Surprisingly, the recording of thoracoabdominal dimensions by means of external sensors, such as magnetometers [45], strain gauges [22] and inductive plethysmography [16], did not show any significant change in the shape of the chest or abdomen. However, a more recent study has combined transverse sections of the chest and abdomen obtained by computed tomography (CT) with central blood volume measurement by dye dilution and FRC recording by multiple breath washout; using this complex technique, a pattern of changes was noted during anaesthesia with muscle paralysis and mechanical ventilation [18]. Cranial shift of the diaphragm was confirmed and, in addition, it was seen that the transverse cross-sectional area of the thorax was reduced slightly. At the same time, blood was moved from the thorax and, together with smaller amounts of blood from the extremities, was pooled probably in the abdomen [15]. The net effect of all these changes was a decrease in intrathoracic volume by approximately 0.8 litre. However, the net effect on the *external* dimensions of chest and abdomen was a reduction in volume of only 0.1-0.2 litre. Obviously, these small changes may be undetected by surface sensors.

Using advanced CT technology, Krayner and co-workers [24] obtained several simultaneous CT scans of the chest and abdomen in anaesthe-

KEY WORDS

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tized subjects. They noticed also a reduced thoracic cross-sectional area, but also a caudad displacement of the diaphragm. It is not known what factors cause caudad shift of the diaphragm in the anaesthetized, paralysed subject at zero end-expiratory pressure.

Airway closure

In the late 1960s, Milic-Emili and co-workers [28] observed that airways close during deep expiration. In view of the observed reduction in FRC, this soon raised the question as to whether airway closure occurs during anaesthesia. In 1972, Don, Wahba and Craig [9] found that some gas was trapped during anaesthesia, and that it could be released only by deep inflations. This clearly suggested the occurrence of airway closure during anaesthesia. Confirmation followed some years later [13, 17], although conflicting results have also been presented [23]. In general, no good correlation between the degree of airway closure and magnitude of gas exchange impairment during anaesthesia has been shown [3, 17]. On the other hand, a decrease in FRC during anaesthesia to less than the *awake* closing capacity (CC) (the lung volume at which airways close) was accompanied by a significantly larger shunt (mean 11%) than when FRC during anaesthesia was larger than awake CC (mean 2%) [10]. It may be concluded, therefore, that there is evidence of airway closure during anaesthesia, but that its significance regarding gas exchange impairment has not yet been established. There may be additional, more important, functional disturbances that impede arterial oxygenation.

Atelectasis

The results of our study on chest-abdomen dimensions indicated a considerable reduction in thoracic volume [18]. We therefore considered if the lung tissue could be affected by such a volume decrease. In order to study lung morphology non-invasively in the human subject, we again used CT scanning with transverse exposures of the chest as shown in figure 1 [6]. The patient lay supine on the tomograph table and held his breath at the FRC level during the 5-s exposure of x-ray tube rotation around the body.

In the mid panel of figure 1, a transverse exposure of the chest in an awake subject is shown. The thorax is viewed from below, with the right lung to the left. Both lungs are well aerated and a few pulmonary vessels can be seen in the

lower part of the lungs. There are no other dense regions within the lungs.

Fifteen minutes after induction of anaesthesia, muscle paralysis and connection to a ventilator, the patient displayed clear changes compared with the awake state. In a CT scan identical to that taken before anaesthesia (fig. 1, lower panel) it may be seen that the diaphragm (seen as the large white area in the middle of the right lung) has been pushed cranial. This displacement has been a consistent finding in more than 150 patients examined and is to a certain degree at variance with observations made by Krayner and colleagues [24]. Moreover, in the dependent regions of both lungs, dense areas can be seen. These areas have an attenuation factor which corresponds to blood and connective tissue and indicates lack of air. Similar dense areas in dependent lung regions have not been seen in any of our awake subjects, whereas during anaesthesia it is a recurrent finding and appears in approximately 90% of subjects with normal lungs [39].

The dense areas may be reduced or eliminated by applying positive end-expiratory pressure (PEEP) of 10 cm H₂O [6] (fig. 2). Interestingly, on discontinuation of PEEP, the densities reappeared within 1 min. Also, the dense areas developed to the same extent, whether the inspired oxygen concentration was 40% or 100%. These observations do not support the concept of slow absorption of gas from closed-off lung units, which is the mechanism normally ascribed to formation of atelectasis (so-called absorption atelectasis). Furthermore, when a patient is turned from the supine to the lateral position, the dense areas remain in the same anatomical positions as before in the lower lung. This suggests that the dense region is not composed of pleural or interstitial fluid, as both these would be expected to move to the new dependent region of the lung.

To obtain a more detailed picture of the dense areas, we have tested different animal models. We found that anaesthetized sheep in the dorsal recumbent position developed dense areas in dependent lung regions, similar to those seen in the anaesthetized human [19]. At the end of each experiment the lungs were removed and tissue samples subjected to microscopy. It was observed that the radiologically dense areas corresponded to completely collapsed (atelectatic) lung with only moderate vascular congestion and no clear interstitial oedema [19]. We assume that the dense lung areas in man have the same microscopic

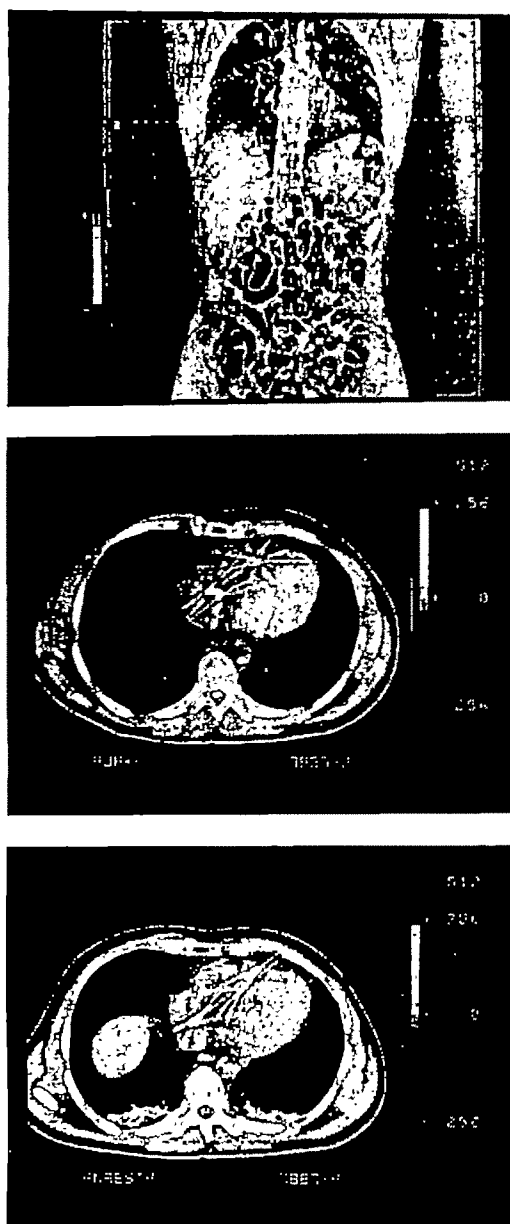


FIG. 1. *Upper panel*: Frontal view of the chest and abdomen with broken line indicating the position of the transverse CT section. The exposure level was fixed relative to the spine when measurements were repeated, for example during different anaesthetic conditions. *Mid panel*: Transverse CT section in an awake subject. The lungs are seen from below, with the right lung to the left. Note the absence of dense areas in the lungs, except for a few vessels. A catheter is positioned in the heart and produces star-like radiating beams (a reconstruction error). *Lower panel*: the same subject as above, approximately 15 min after induction of anaesthesia and muscle paralysis. Note the appearance of dense areas in the dependent region

appearance, and thus conclude that they represent atelectasis. We hypothesize that they are caused by a loss of such forces as normally support the lung and consequently have termed the dense areas "compression atelectasis".

Anaesthetic regimen and compression atelectasis

The anaesthesia used in the studies described above included both i.v. (barbiturate) and inhalation (halothane) agents; measurements were not made until muscle paralysis had been produced with pancuronium. To determine if atelectasis was caused by the anaesthetic agent or by muscle paralysis, we studied subjects whose anaesthesia was induced by inhalation of halothane from a face mask, without other drugs or neuromuscular block, and without tracheal intubation. We found that atelectasis in dependent lung regions developed during spontaneous breathing, although there was a further small increase in the atelectatic area after induction of neuromuscular block [37].

We also questioned if the anaesthetic agent acted directly on the pulmonary alveoli, or if the effect was mediated centrally (or via the blood). This was determined by comparing the effects of inhalation and of i.v. anaesthesia. No significant difference in the size of the atelectatic area was seen in patients anaesthetized with an inhalation agent (halothane) or with an i.v. drug (barbiturate). Also, the addition of halothane to the inspired gas after previous induction of anaesthesia with a barbiturate did not increase the area of atelectasis [37]. Similar formation of atelectasis has been seen during inhalation anaesthesia with enflurane and isoflurane, and during anaesthesia with the new i.v. agent propofol [unpublished data]. However, to date one anaesthetic, ketamine, has been shown not to produce atelectasis [43]. In this case, however, atelectasis developed as soon as muscle paralysis was produced by pancuronium. Thus we may conclude that most (but not all) anaesthetic drugs cause formation of atelectasis in dependent lung regions. It also appears that muscle paralysis may lead to atelectasis, and increase the area of atelectasis in patients who have already developed lung densities during anaesthesia with spontaneous breathing.

of both lungs, indicating development of atelectasis. The white area in the middle of the right lung is the cranially displaced diaphragm.

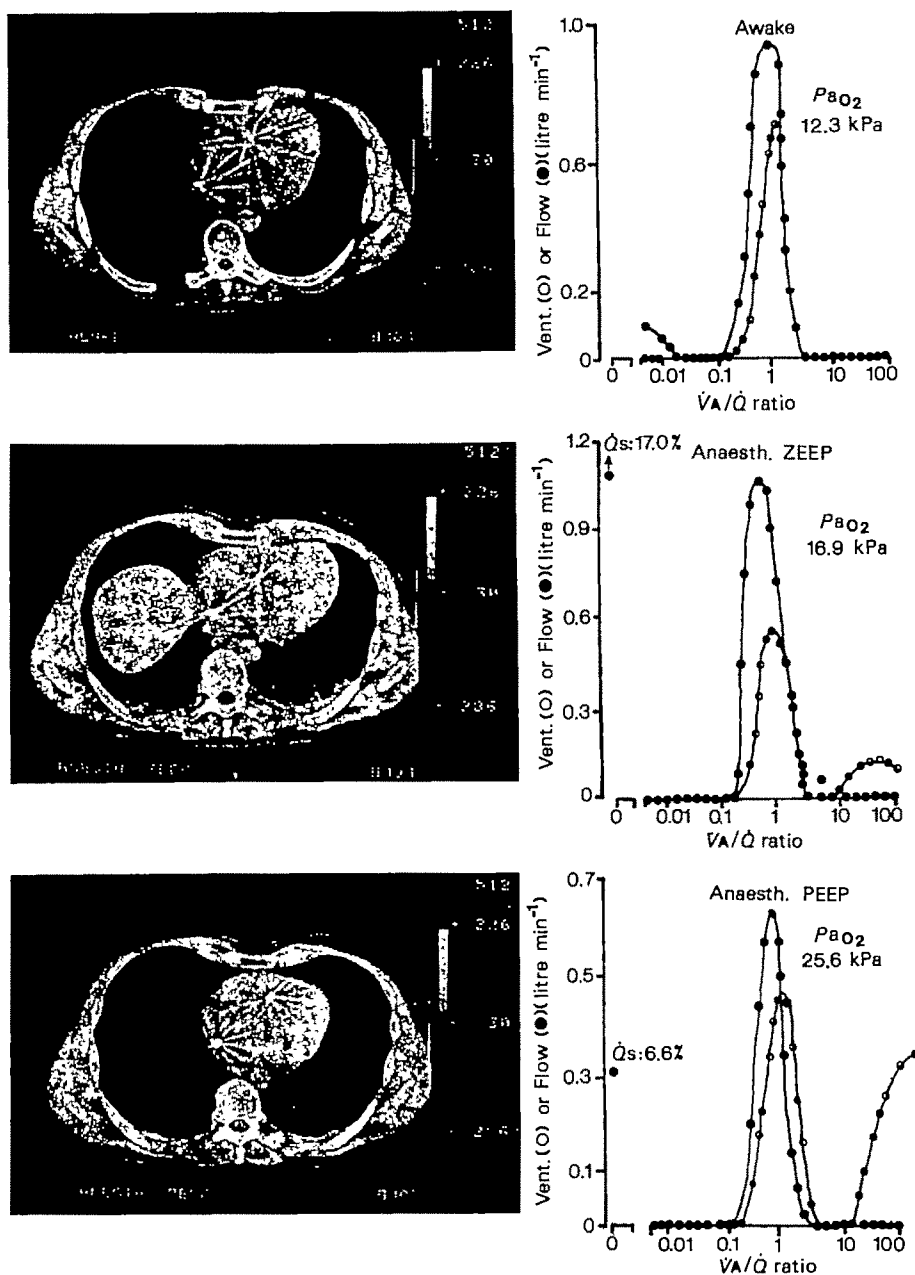


FIG. 2. Transverse CT sections of the chest and $\dot{V}_A/\dot{Q}$ distributions in a patient when awake (upper panel), during anaesthesia and muscle paralysis but zero end-expiratory pressure (ZEEP) (mid panel) and during anaesthesia with a positive end-expiratory pressure (PEEP) of 10 cm H₂O (lower panel). Vent. = Ventilation; Flow = blood flow. In the awake state there were no densities in dependent lung regions, and the $\dot{V}_A/\dot{Q}$ distribution was essentially normal and centred on a $\dot{V}_A/\dot{Q}$ ratio of 1. A minor "low" $\dot{V}_A/\dot{Q}$ mode can be seen. During anaesthesia, rather large dense regions are seen in both dependent lung regions, and the diaphragm can be seen as a large, white area in the right lung field. Significant shunt has developed, and small mode within high $\dot{V}_A/\dot{Q}$ regions. During PEEP, the atelectatic areas in dependent lung regions have been reduced, as has the shunt. (The effect of PEEP on shunt may vary from patient to patient.) The high $\dot{V}_A/\dot{Q}$ mode has increased further in size. This mode may be explained by poor perfusion of upper lung regions. (The upper four panels are reproduced from Hedenstierna and colleagues [14], by courtesy of the editor of *Acta Anaesthesiologica Scandinavica*.)

Deadspace and elimination of carbon dioxide

Some inspired gas does not participate in gas exchange because it is in airways (anatomical or series deadspace) or in non-perfused alveoli (alveolar or parallel deadspace). The elimination of carbon dioxide is less efficient if deadspace is increased. In 1957, Severinghaus and Stupfel [36] showed that anaesthesia caused impaired elimination of carbon dioxide. Using a single breath washout technique, Nunn and Hill [31] found that the anatomical deadspace was unchanged during anaesthesia, indicating that the alveolar deadspace must have been increased. In general, impaired elimination of carbon dioxide is easily overcome by increasing ventilation, and it is seldom a problem in routine anaesthesia with mechanical ventilation.

Arterial oxygenation

Arterial oxygenation is impaired in most patients during anaesthesia, with either spontaneous or controlled ventilation [27, 31, 41]. It is generally held that the impairment of arterial oxygenation during anaesthesia is more severe in the elderly [30]. Obesity is associated with reduced oxygen saturation [44], and smokers show greater impairment of gas exchange than non-smokers [11]. On the basis of pulmonary arterial and mixed venous oxygen content, venous admixture can be calculated. It gives an overall indication of gas exchange impairment, but does not permit detailed analysis of the underlying mechanisms. In various studies, venous admixture has been found to average 10% during anaesthesia (for a review, see [30]).

Ventilation/perfusion relationships

It was not until the end of the 1970s and beginning of the 1980s that more detailed analyses of the ventilation/perfusion ($\dot{V}_A/\dot{Q}$) relationships were made during anaesthesia. Using a multiple inert gas elimination technique, the $\dot{V}_A/\dot{Q}$ relationships were studied in young healthy volunteers [34]. They displayed only a small $\dot{V}_A/\dot{Q}$ mismatch during anaesthesia, with increased scatter of $\dot{V}_A/\dot{Q}$ ratios, and the appearance of a small shunt [34]. On the other hand, in a similar age group, Prutow and co-workers described a much larger shunt averaging 8% during anaesthesia and before surgery [33].

In a study by Bindsløv and co-workers [4] of a middle-aged group of patients during anaesthesia,

shunt was again found to increase from 1% awake to approximately 8%, and there was widening of $\dot{V}_A/\dot{Q}$ distribution, but little or no perfusion of low $\dot{V}_A/\dot{Q}$ regions (i.e. perfusion in excess of ventilation ($0.005 < \dot{V}_A/\dot{Q} < 0.1$)). In a group of elderly patients with more marked deterioration in pulmonary function, anaesthesia caused considerable widening of $\dot{V}_A/\dot{Q}$ distribution, with large increases both in low $\dot{V}_A/\dot{Q}$ regions and in shunt [11]. It may be concluded, therefore, that in the healthy young or middle-aged patient the major $\dot{V}_A/\dot{Q}$ disturbance during anaesthesia is pure shunt with only a moderate contribution by blood coming from "underventilated" lung zones.

Atelectasis and gas exchange impairment

When radiocontrast dye is injected into a central vein it may be seen that the atelectatic area, as assessed by CT scanning, is perfused by blood from the pulmonary artery [38]. This suggests that atelectasis acts as a region of shunt. Recently, the $\dot{V}_A/\dot{Q}$ distributions have been correlated with CT-scans of the chest during anaesthesia. In subjects with healthy lungs the major $\dot{V}_A/\dot{Q}$ disturbance was again the appearance of shunt, with very little change to low $\dot{V}_A/\dot{Q}$ distribution. In a group of 45 patients studied awake and during anaesthesia with both CT scanning and multiple inert gas elimination, a strong correlation was found between the magnitude of shunt and the size of atelectasis (fig. 3; see also [42]). In a few patients who did not develop any atelectasis during anaesthesia, no shunt and no clear impairment of arterial oxygenation were seen. A PEEP of 10 cm H₂O reduced the size of the atelectatic area, but the effect on shunt varied:

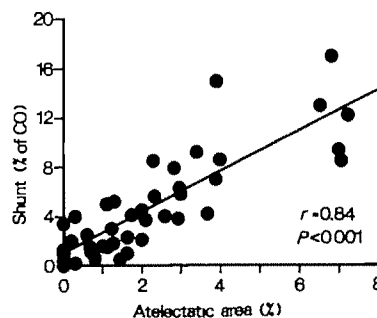


FIG. 3. Plot of shunt ($\dot{Q}_s$) as a percentage of cardiac output vs the atelectatic area as a percentage of the total intrathoracic area, during inhalation anaesthesia with muscle paralysis and mechanical ventilation. (Data pooled from various studies; see also [42].)

in some patients it decreased and in others it increased. This is similar to the varying effects of PEEP on $P_{a_{O_2}}$ described by Hewlett and colleagues [20]. Shunt maintained during PEEP can probably be accounted for by redistribution of blood flow towards dependent, persistent atelectatic areas [46].

In summary, these studies confirm the previous observations that shunt is a major cause of gas exchange impairment during anaesthesia in subjects with healthy lungs, and that this can be explained by perfusion of blood through the atelectatic zone in dependent lung regions. It is also interesting to note that the i.v. anaesthetic

agent, ketamine, which does not reduce muscle tone as do other anaesthetics, did not produce atelectasis or shunt, whereas both were seen when the same patients were paralysed with a neuromuscular blocking drug [43].

By means of the same technique as described above, patients with chronic obstructive lung disease have been studied awake and during anaesthesia, in order to elucidate the more severely impaired gas exchange that these patients are known to suffer during anaesthesia [L. Gunnarsson and co-workers, in preparation]. Surprisingly, these patients developed no, or only little atelectasis during anaesthesia; concomitantly, no or

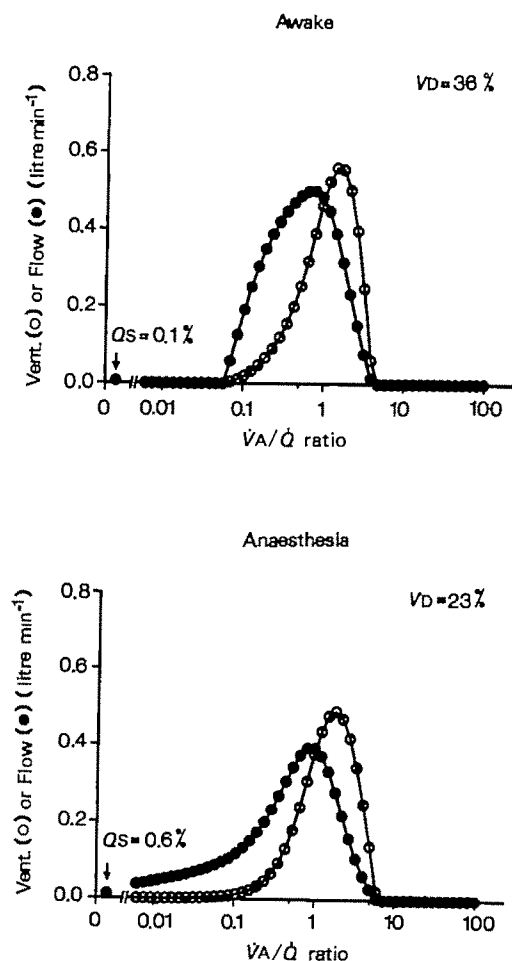


FIG. 4. Ventilation-perfusion distributions and CT scans in a patient with severe chronic obstructive pulmonary disease; awake (upper panels) and during inhalation anaesthesia (lower panel). Note the large transverse lung area awake, suggestive of hyperinflation, and the maintained area during anaesthesia (compare with the lung healthy subjects in figures 1 and 2). Note also that there is no atelectasis and almost no shunt either awake or anaesthetized. On the other hand, "low" $\dot{V}_A/\dot{Q}$ regions ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) appeared during anaesthesia (from Gunnarsson and co-workers [in preparation]).

only minor shunt was seen. This is consistent with atelectasis being the sole or major cause of shunt. On the other hand, severe $\dot{V}_A/\dot{Q}$ mismatch was seen in these subjects, with a large part of perfusion going to lung regions characterized by low $\dot{V}_A/\dot{Q}$ ratios. An example is given in figure 4. The apparent protection against atelectasis and the factors causing the large regions of low $\dot{V}_A/\dot{Q}$ are open to speculation, but it is assumed that chronic hyperinflation may change the mechanical behaviour of the lungs, and that airways close during expiration before alveoli begin to collapse. By this means, prompt formation of atelectasis is prevented. However, ventilation is reduced also in relation to perfusion, producing regions with low $\dot{V}_A/\dot{Q}$. It can be anticipated that, during prolonged anaesthesia, these regions of low $\dot{V}_A/\dot{Q}$ may be transformed into atelectatic shunt regions by uptake of gases by the blood faster than the delivery to the alveoli via the airways.

Hypoxic pulmonary vasoconstriction

Release or attenuation of hypoxic pulmonary vasoconstriction (HPV) during anaesthesia has frequently been considered a mechanism of impaired gas exchange during anaesthesia. Several inhalation anaesthetics have been found also to inhibit HPV in isolated lung preparations [40], but no such effects have been seen with i.v. anaesthetics (barbiturates) [5]. Results from human studies are inconsistent, presumably because the HPV response is obscured by simultaneous changes in cardiac output, myocardial contractility, vascular tone, blood volume distribution, blood pH and carbon dioxide tensions, and lung mechanics [26]. However, it should be made clear that attenuation of HPV requires an underlying disturbance in lung function for it to produce impaired arterial oxygenation. Unless such disturbances exist, release or attenuation of the hypoxic vasoconstrictor response does not produce any impairment of gas exchange. As atelectasis is known to be produced during anaesthesia, release or attenuation of HPV may be said to increase blood flow through the atelectatic zone and thus increase shunt. However, the commonly used inhalation anaesthetics abolish only part of the HPV response at clinical concentrations of the agent. For instance, isoflurane inhaled at a concentration of 1 MAC attenuates HPV by no more than 25% [21].

CONCLUSION

It may be concluded that the well-known impairment of gas exchange during anaesthesia is, to a large extent, attributable to early formation of atelectasis in dependent lung regions, which in turn produces shunt. In the absence of atelectasis, gas exchange may be more or less preserved. Why atelectasis occurs and if airway closure is an important factor, remain subjects for future study. Respiratory muscle function may play a key role in the impairment of gas exchange during anaesthesia. Its preservation, for example during ketamine anaesthesia, is accompanied by more or less normal gas exchange.

Protection against dependent atelectasis, without any impediment to the pulmonary circulation, should be a future goal in improving gas exchange during anaesthesia.

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EFFECTS OF NEBULIZED LIGNOCAINE ON THE INTRAOCULAR PRESSURE RESPONSES TO TRACHEAL INTUBATION

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SUMMARY

We have examined the effect of preoperative administration of nebulized lignocaine or saline on the intraocular pressure (IOP) response to tracheal intubation in 20 adults. In the saline group, tracheal intubation was associated with a significant increase in IOP above control and preintubation values ($P < 0.01$); in the lignocaine group there was no change in IOP following intubation. After intubation, IOP was significantly less in the lignocaine group than in the saline group ($P < 0.05$).

KEY WORDS

Eye: intraocular pressure. Anaesthetics local: lignocaine.

Laryngoscopy and tracheal intubation induce an increase in arterial pressure and IOP [1]. The administration of nebulized lignocaine before induction of anaesthesia has been shown to reduce the pressor response to tracheal intubation [2-4], but the effect of this manoeuvre on IOP has not been studied. We have examined, therefore, the influence of nebulized lignocaine on the haemodynamic and IOP changes caused by tracheal intubation.

METHODS AND RESULTS

The study was approved by the District Medical Ethics Committee. Informed consent was obtained from 20 ASA class I and II patients (12 male) undergoing routine ophthalmic surgery. They were allocated randomly to receive either saline ($n = 10$) or lignocaine 6 mg kg^{-1} ($n = 10$). All patients were premedicated with oral diazepam. In the anaesthetic room, each patient was given 0.15 ml kg^{-1} (maximum dose 10 ml) of

the test solution using an Acorn nebulizer (part No. 1049, Medic-Aid, U.K.). Anaesthesia was induced with thiopentone 5 mg kg^{-1} followed by atracurium 0.6 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained by controlled ventilation with 65% nitrous oxide in oxygen via a Bain system. End-tidal carbon dioxide concentration was maintained at $5 \pm 0.1\%$ (ventilatory frequency about 12 b.p.m.) and tidal volume 10 ml kg^{-1} (monitored by infra-red carbon dioxide analyser and Wright's respirometer, respectively). After the study period, 1% enflurane was added and droperidol $2.5\text{--}5 \text{ mg}$ given i.v. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate 50 and $10 \mu\text{g kg}^{-1}$, respectively.

Heart rate and arterial pressure were monitored by electrocardiogram and automatic pressure device, respectively. IOP was measured in the unoperated normal eye by a Perkins applanation tonometer. Heart rate, arterial pressure and IOP were measured before nebulization of the test solution, after nebulization, before intubation, immediately after intubation, 2.5 and 5 min thereafter (table I). Venous blood samples were obtained at corresponding times and at 10 and 20 min after nebulization for measurement of plasma concentrations of lignocaine using high pressure liquid chromatography. Parametric data were analysed within and between groups by

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TABLE I. Mean (SD) values of IOP, arterial pressure and heart rate. Significant change from *control and †preintubation ($P < 0.05-0.001$). 1 = Before nebulization of test solution; 2 = after nebulization; 3 = before intubation; 4 = immediately after intubation; 5 = 2.5 min after intubation; 6 = 5 min after intubation

	1	2	3	4	5	6
IOP (mm Hg)						
Saline	11.3 (3.5)	11.2 (2.5)	8* (3.6)	19.3*† (6)	15.2*† (4.5)	13† (4.9)
Lignocaine	12.9 (2.8)	11.6* (2.8)	10.6* (4.4)	10.4 (4.9)	7.1* (3.5)	6*† (3.3)
SAP (mm Hg)						
Saline	147.2 (20.5)	149.6 (20.5)	143 (32.6)	190*† (29.7)	162* (26.1)	143.6 (31.5)
Lignocaine	165.5 (40.7)	160.8 (36.3)	142.4* (36.3)	154.3 (36.3)	145.6 (28.9)	129.5* (23.1)
DAP (mm Hg)						
Saline	85.4 (13.7)	84.3 (12.7)	86.1 (20.7)	110*† (23.1)	96.8 (17.1)	85.6 (15.7)
Lignocaine	98.6 (17.9)	97.7 (19.7)	86.9 (13)	99.9† (15.3)	84.6* (7.41)	80.4* (9.5)
HR (beat min ⁻¹)						
Saline	73.8 (6.3)	68.1 (6.4)	87.4* (17.2)	99.9*† (21)	93.1* (15.4)	86.1* (16.9)
Lignocaine	81.9 (10.8)	84.1 (15.4)	96* (12.4)	94.8* (11.4)	83 (15.2)	80.4 (15.3)

paired and unpaired Student's *t* test, respectively, and non-parametric data by the Mann-Whitney *U* test.

There were no significant differences in mean prenebulization values between the saline and lignocaine groups for age (70 and 62 yr, respectively), weight (65 and 70 kg) or sex distribution of patients (table I). Following intubation in the saline group, there were increases in IOP, heart rate and arterial pressures to values significantly greater than control ($P < 0.01$) and preintubation values ($P < 0.05$). In comparison, post-intubation IOP, heart rate and systolic pressures in the lignocaine group were not significantly different from control or preintubation values; indeed, IOP was significantly less than control. Although heart rate increased significantly above control following induction ($P < 0.01$), post- and pre-intubation values were not significantly different. Only a small, albeit significant ($P < 0.05$) increase in diastolic pressure was noted, immediately after intubation.

Following intubation, all IOP values in patients who received lignocaine were significantly lower than those given saline ($P < 0.001$). Post-intubation systolic and diastolic pressures in the lignocaine group remained less than those in the

saline group immediately after intubation and at 2.5 min thereafter ($P < 0.05$). Mean peak plasma concentration of lignocaine after nebulization was 1.07 (SD 0.53) $\mu\text{g ml}^{-1}$, decreasing to 0.56 (0.21) $\mu\text{g ml}^{-1}$ at the end of the period of study.

COMMENT

We have demonstrated that tracheal intubation produced a significant increase in IOP and haemodynamic state, confirming previous studies [1]. Several techniques have been used to modify the pressor response to intubation [5], but none is completely successful.

Previous studies [2, 3] have demonstrated that administration of nebulized lignocaine before operation did not abolish the pressor response to tracheal intubation. Our lignocaine group demonstrated a more stable haemodynamic response. This difference may be a reflection of the dose of lignocaine used and our technique of administration. Clay and Clarke [6] have reported that, during nebulization, 15% of the first part of a dose is deposited in the body and only 7–12% reaches the airways. Previous studies with nebulization involved smaller doses of lignocaine than that used here, a face mask or a short period of nebulization. Despite our use of a larger dose

and more efficient method of administration, the plasma concentrations were lower than toxic values ($5-9 \mu\text{g ml}^{-1}$). The greatest concentration recorded was $2.3 \mu\text{g ml}^{-1}$, similar to those reported in other studies [3, 4].

Transient changes in IOP are probably of little importance in healthy individuals. However, such changes may be hazardous in patients with a lacerated globe or glaucoma. None of the studies involving lignocaine nebulization examined changes in IOP. In our study, mean IOP increased substantially above control after intubation in the control group, but there was no change in the group given lignocaine. A slight decrease in arterial pressure, caused possibly by lignocaine, was noted following nebulization and may account for the decrease in IOP after nebulization. However, this may have been caused by oxygen, which was used as the sole gas to nebulize lignocaine [5]. Reduction in IOP following induction and intubation may have resulted from the effects of thiopentone or absence of reflex pressor responses to the stimulus of intubation as a result of local anaesthesia of the airway.

Several factors affect IOP during anaesthesia. In our study, excessive inflation pressure was avoided, normocapnia and normoxia were maintained and the patient remained supine to prevent hydrostatic changes in IOP.

In a previous study [3] a mixture of viscous and aqueous lignocaine was administered via a modi-

fied Bird nebulizer. This technique is not suitable for routine use, and inhalation of viscous lignocaine may cause obstruction of small airways, hence it cannot be recommended at present. Our nebulization technique is simple, but acceptability to patients demands full explanation and reassurance regarding loss of pharyngeal reflexes.

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PREVENTION OF POSTOPERATIVE PAIN BY BALANCED ANALGESIA

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AND H. KEHLET

SUMMARY

Fourteen patients undergoing colorectal surgery received an intraoperative afferent neural block with combined intrathecal and extradural local anaesthetics plus a balanced postoperative low-dose regimen of extradural bupivacaine 10 mg h^{-1} -morphine 0.2 mg h^{-1} and systemic piroxicam 20 mg/24 h . Postoperative pain, assessed repeatedly during the initial 48 h, was prevented during rest, mobilization from the supine to the sitting position and during walking, in all but one patient; slight pain was observed intermittently during coughing in four patients.

KEY WORDS

Anaesthetic technique: extradural, spinal. Pain: post-operative.

Treatment of postoperative pain has improved during recent years. The combination of analgesic regimens such as extradural local anaesthetics and opioids [1, 2] has improved analgesia with the use of smaller doses of drugs. However, total pain relief could only be obtained with relatively high doses of local anaesthetics and opioids [3], thus carrying the risk of severe side effects. Experimental studies suggest that neural afferent block applied before injury may reduce postinjury hypersensitivity to pain [4]. These findings led subsequently to the hypothesis that postoperative pain may be ameliorated by neural block during operation [5]. We have studied, therefore, the analgesic effect of intraoperative afferent neural block through the combined use of intrathecal and extradural local anaesthetics, plus continuous postoperative low-dose bupivacaine and morphine extradurally and systemic piroxicam in patients undergoing major colonic surgery.

METHODS AND RESULTS

We studied 14 patients (four male), mean age 69 yr (range 42-80 yr), mean body weight 68 kg (range 47-98 kg) and mean height 166 cm (range 156-179 cm) undergoing colorectal surgery. All patients had a low midline incision, extended above the umbilicus during right hemicolectomy and when the splenic flexure had to be mobilized (six patients). All patients were ASA group I or II, without signs of endocrine disease. Patients with symptoms of infection within 2 weeks before operation or history of drug or alcohol abuse were not included. Informed consent was obtained and the study was approved by the local Ethics Committee.

On the evening before surgery and 1 h before surgery, the patients received piroxicam 40 mg by mouth. On the following two days, piroxicam 20 mg was administered rectally each morning. All patients received diazepam 5-10 mg by mouth as premedication. Before induction of anaesthesia, ephedrine 25 mg was given i.m., with increments of 5-10 mg i.v. during operation if the systolic arterial pressure decreased to less than 70 % of the value before operation. An extradural catheter was inserted at a level of T9-T12, depending on the site of operation and tested with 0.75 % bupivacaine 2 ml. In order to obtain a continuous spinal anaesthesia during the operation, a spinal catheter (Portex 18-gauge) was inserted at L3-4 and 5 % lignocaine 2 ml injected in order to provide sensory analgesia from T4 to S5. If

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necessary, incremental doses of lignocaine 25 mg were injected to obtain this level. Seven millilitre of 0.75% plain bupivacaine plus morphine 2 mg was then injected extradurally, followed by continuous extradural infusion of a mixture of 0.25% bupivacaine plus morphine 0.05 mg ml⁻¹, 4 ml h⁻¹ for 48 h using a Pharmacia Deltec pump. During operation, 5% lignocaine 0.5 ml was given every 45 min and 0.75% bupivacaine 4 ml every 60 min in the spinal and extradural catheters, respectively. The spinal catheters were removed at the end of surgery.

General anaesthesia was induced with thiopentone and maintained with 0.2–1% enflurane and nitrous oxide with oxygen. Tracheal intubation was facilitated with suxamethonium; no muscular blocking agents or systemic opioids were administered subsequently.

Pain scores on a four-point scale (no pain, mild pain, moderate pain, and severe pain) at rest, during cough and mobilization from the supine to the sitting position and during walking, and levels of sensory analgesia (pinprick bilaterally) and motor block on a scale (Bromage) 0 = no paralysis, to 3 = total paralysis were assessed 4, 8, 12, 24, 30 and 48 h after surgical incision by two of the authors. After operation, morphine 5 mg i.v. was given if requested by the patient. All patients had a bladder catheter inserted during surgery and subsequently for 48 h.

Blood samples for analysis of cortisol (radioimmunoassay) and glucose (glucose oxidase method) were taken before induction of anaesthesia, at surgical incision and 1, 4, 8, 24 and 48 h after surgical incision.

Changes in plasma cortisol and glucose concentrations were evaluated by Friedman's two-way analysis of variance. $P < 0.05$ was considered statistically significant.

Mean duration of surgery was 168 min (range 105–330 min). Administration of i.v. fluid (isotonic saline) amounted to 3400 ml (range 1500–5800 ml). Total mean dose of ephedrine was 57 mg (range 30–95 mg).

All patients were totally pain free during the initial 48-h postoperative period at rest, except one patient who had slight pain at two assessments (fig. 1). During cough three patients had slight, and one moderate, pain at six assessments. During mobilization in bed from the supine to the sitting position, all patients were pain free from 4 to 48 h after skin incision, except one patient with intermittent slight or moderate pain at 8, 30 and

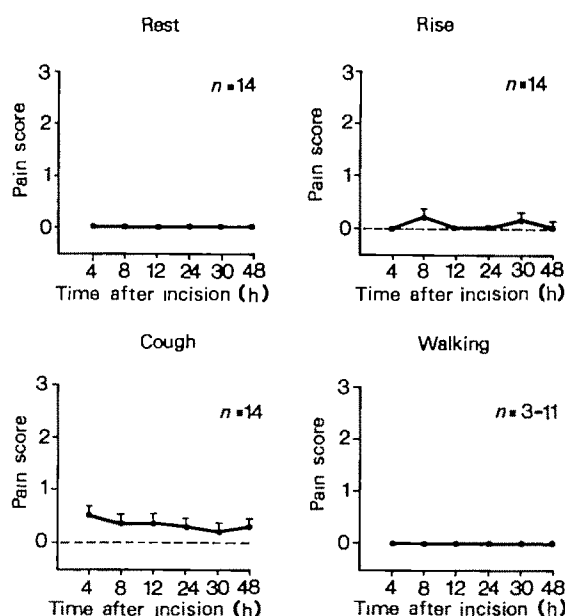


FIG. 1. Mean (SEM) pain scores at rest, during cough, rising from the supine to the sitting position and during walking in 14 patients undergoing colonic surgery during combined intrathecal extradural and general anaesthesia plus low-dose extradural bupivacaine-morphine and systemic piroxicam.

48 h, and one patient with slight pain at 8 h. Walking was not possible 8 h after skin incision in one patient and at 24 h in another because of residual motor block (1–2 on the Bromage scale) and not at 12 h in two because of dizziness, in one with drainage and three with bluntness. Four patients walked pain free at from 4 to 8 h after skin incision. From 24 to 48 h, 11 patients were pain free during normal walking, but the three remaining patients who were pain free could not walk freely without assistance because of dizziness or drainage. None of the patients had muscular paralysis (0 on the Bromage scale) 24 h after the surgical incision.

Only one patient, a 42-yr-old man weighing 98 kg and with an extended supra-umbilical incision, received additional analgesics (morphine 5 mg on one occasion) during the 48-h period after operation. This was the patient who had slight pain during rest and slight to moderate pain during cough and mobilization.

Mean level of sensory analgesia was T3–S5 before operation. Sensory analgesia decreased slightly during the first days after operation, and 48 h after operation 12 patients had maintained sensory analgesia (mean level T6–T11), but two

patients had no detectable sensory analgesia to pinprick.

There was no significant change in plasma concentration of cortisol: mean 369 (SEM 22) nmol litre⁻¹ before operation compared with a maximum of 517 (83) nmol litre⁻¹ after operation. Plasma concentrations of glucose increased after induction of anaesthesia and before surgery, from 4.5 (0.2) to 5.3 (0.3) mmol litre⁻¹, values remaining increased ($P < 0.05$) throughout the study.

One patient developed a post-dural puncture headache; no other complications related to anaesthesia or postoperative analgesia were observed.

COMMENT

In the present study, complete pain relief during rest and mobilization, but not during cough, was achieved with a regimen of low-dose extradural bupivacaine plus morphine and systemic non-steroid anti-inflammatory agent (piroxicam) in almost all of the 14 patients studied during major abdominal surgery.

There may be several explanations for the success of this regimen. Preinjury neural block by nerve section or local anaesthesia has been shown to reduce post-injury pain hypersensitivity in experimental studies [4]. If confirmed in humans, these findings may suggest that reduction of post-injury pain hypersensitivity by effective intra-operative neural block may facilitate postoperative pain relief. Another explanation may be the concomitant use of a non-steroid anti-inflammatory agent which may have an additive or synergistic analgesic effect with the extradural analgesic regimen.

The regional anaesthetic regimen prevented the

normal increase in plasma cortisol. This has not been observed before during colonic surgery [6] and suggests that the regimen provides good afferent block. The increase in plasma glucose observed before surgery may have been caused by ephedrine, although such an effect would not be expected to continue long into the postoperative period.

The reduced demand for analgesics with preservation of pain relief may be important in reducing side effects and thereby the need for postoperative surveillance. The concept of balanced analgesia may have an important impact on postoperative convalescence and morbidity, and warrants further study.

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CLINICAL OBSERVATIONS ON THE NEUROMUSCULAR BLOCKING ACTION OF ORG 9426, A NEW STEROIDAL NON-DEPOLARIZING AGENT

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SUMMARY

The neuromuscular blocking effects of Org 9426, the 2-morpholino, 16-allyl-pyrrolidino derivative of the 3-desacetoxy analogue of vecuronium have been investigated in anaesthetized patients. Based on data from a pilot study, two doses, 250 and 500 $\mu\text{g kg}^{-1}$ (estimated as the ED_{90} and $2 \times \text{ED}_{90}$, respectively) were chosen. Org 9426 appeared to be six to eight times less potent than vecuronium and showed a faster rate of development of neuromuscular block, with good to excellent intubation conditions within 60 s after administration of a dose of 500 $\mu\text{g kg}^{-1}$. The duration of action and the recovery index appeared to be similar to those of vecuronium. Side effects were not noted. Org 9426 may have advantages over existing non-depolarizing neuromuscular blocking agents with respect to rate of development of good intubating conditions, and is stable in aqueous solutions.

KEY WORDS

Neuromuscular relaxants: Org 9426, vecuronium. Intubation, tracheal.

Nearly 50 years after the introduction of curare into clinical practice, the search for better drugs led to clinical testing and development of a great number of non-depolarizing neuromuscular blocking agents. Recently developed blocking drugs are of intermediate duration and, to a major extent, free from side effects. However, even after intubating doses, onset times are relatively slow compared with that of suxamethonium. The clinical need for a "clean" non-depolarizing agent with a rapid onset time and a brief duration of neuromuscular blocking effect led to the development of Org 9426. In animal pharmacology,

the onset time of Org 9426 appeared to be significantly faster than that of vecuronium [1]. Duration and recovery time were equal or slightly shorter than that of vecuronium. In addition, Org 9426 showed cardiovascular stability and it is stable in aqueous solution.

We have investigated the potency and the time course of action of Org 9426 at doses of 250 and 500 $\mu\text{g kg}^{-1}$ in anaesthetized patients.

METHODS AND RESULTS

We studied 22 ASA I and II patients (aged 18-50 yr) who gave informed consent to participate in the study which was approved by the local Medical Ethics Committee. Premedication consisted of midazolam 0.1-0.15 mg kg^{-1} by mouth 1 h before induction of anaesthesia with thiopentone 4-6 mg kg^{-1} and fentanyl 3-5 $\mu\text{g kg}^{-1}$. Maintenance was with a gas mixture of 65% nitrous oxide in oxygen and supplements of fentanyl and thiopentone. Tracheal intubation was performed immediately after induction following topical lignocaine (250- $\mu\text{g kg}^{-1}$ group) or 1 min after Org 9426 (500- $\mu\text{g kg}^{-1}$ group). Thereafter, carbon dioxide partial pressure was maintained at 4-4.6 kPa.

Mechanomyographic measurements were started after induction using the standard ulnar nerve-adductor pollicis muscle technique. Following stabilization of the twitch, patients received either 250 $\mu\text{g kg}^{-1}$ ($n = 11$) or 500 $\mu\text{g kg}^{-1}$

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TABLE I. Degree of block and onset characteristics (mean (SD)) of Org 9426 compared with vecuronium in patients anaesthetized with an i.v. anaesthetic technique and 65% nitrous oxide in oxygen. †Only six patients reached 75% block. ***Significant difference from vecuronium ($P < 0.005$, Wilcoxon's rank sum test)

Agent	Dose ($\mu\text{g kg}^{-1}$)	n	Max. block (%)	Lag time (s)	Onset time to	
					75% block (s)	Max. block (s)
Org 9426	250	11	69 (22)	34 (11)***	94 (51)†	231 (59)
Org 9426	500	11	98 (03)	36 (14)***	68 (30)***	204 (72)
Vecuronium	85	8	100 (00)	71 (34)	155 (78)	216 (96)

($n = 11$) of Org 9426. The magnitude of the block, onset characteristics and time course of action were studied. The intubation conditions 1 min after Org 9426 were evaluated according to the scale (12–3) of Krieg and colleagues [2]. ECG and heart rate were monitored continuously and arterial pressure was measured every 2 min. Lag time and onset times to 75% block and to maximum block (times from end of injection until first twitch depression, 75% block or maximum block, respectively), clinical and total duration (times from end of injection until 25% and 90% recovery of twitch, respectively) and the recovery rate (time elapsing between 25% and 75% recovery of twitch) were measured. Only one dose of Org 9426 was administered. Subsequently, neuromuscular block was maintained, if necessary, using vecuronium.

All results are presented as mean (SD) values (table I). The magnitude of the block was 69 (22) and 98 (3)% for Org 9426 250 and 500 $\mu\text{g kg}^{-1}$, respectively. The clinical duration, recovery index and total duration were, respectively, 5.2 (5.3), 7.9 (2.3), 16.4 (6) min (250 $\mu\text{g kg}^{-1}$) and 21.2 (5), 8.8 (3.1), 33.6 (8.5) min (500 $\mu\text{g kg}^{-1}$). Tracheal intubation performed 1 min after administration of Org 9426 500 $\mu\text{g kg}^{-1}$ was characterized always by easy laryngoscopy and abducted, non-moving vocal cords. Sometimes, some diaphragmatic coughing was noted after completion of the intubation. The intubation score was 3.7 (0.6). Cardiovascular or other side effects were absent. In one patient, a transient disappearance of the P wave was observed 1 min after administration of Org 9426, but without concomitant changes in arterial pressure. Although this event is unlikely to have been related to the drug, an association cannot be excluded.

COMMENT

Comparison of these results with data for vecuronium from an identical study [3] suggests that Org 9426 has approximately 15% of the potency of vecuronium. Comparing the time course of action reveals close similarity between the two drugs [3]. The new compound has the major advantage that it offers good to excellent intubating conditions 1 min after administration of the estimated $2 \times \text{ED}_{90}$ dose. From the mean block of 69% in the 250- $\mu\text{g kg}^{-1}$ group, it may be concluded that a smaller dose may be used for intubation, as the ED_{90} appeared to be within the range of 300–400 $\mu\text{g kg}^{-1}$. However, the intubating dose is probably close to $1.5 \times \text{ED}_{90}$.

The main change in the first phase of development of block is an intriguing finding which justifies further comparative studies of development of block. Possible explanations for this phenomenon include the relatively low neuromuscular blocking potency of this new compound, necessitating the use of a higher molecular load which results in an increase in both the initial concentration gradient and subsequently the transport of molecules of Org 9426 towards the biophase [4]. In addition, simultaneous and more pronounced inhibition of presynaptic nicotinic cholinergic receptors may be responsible for the rapid initial development of neuromuscular block after Org 9426 [5]. Pharmacokinetic factors, especially those governing the rate of distribution of drug to the biophase, may also be involved.

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TWO CASES OF BAROTRAUMA ASSOCIATED WITH TRANSTRACHEAL JET VENTILATION

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SUMMARY

Two patients suffered barotrauma whilst undergoing transtracheal jet ventilation (TTJV). In the first, TTJV was provided by a Sanders injector and in the second it was given by a high frequency jet ventilator. Barotrauma was a consequence of the expiratory pathway becoming blocked. The mechanism of barotrauma and a method of airway pressure monitoring during TTJV are discussed. It is recommended that meticulous care is taken to ensure an adequate path for expiration when jet ventilation is used.

KEY WORDS

Complications; barotrauma. Ventilation: jet, high frequency.

Anaesthesia for head and neck surgery presents special problems. Maintenance of a clear airway, adequate ventilation and good surgical access are of prime importance. Techniques of insufflation or jet ventilation have been described in an attempt to achieve these aims. Two cases of barotrauma are presented; both occurred in patients in whom transtracheal jet ventilation (TTJV) was used.

CASE REPORTS

Patient 1

A female child with Treacher Collins syndrome (mandibulofacial dysostosis) and weighing 9.8 kg presented at the age of 18 months for craniofacial surgery involving reconstruction of the lateral orbital floor and malar area. She exhibited all characteristics of the Treacher Collins syndrome, with downward sloping palpebral fissures towards the outer canthi, sunken cheek bones and a hypoplastic mandible. Previous anaesthesia for palatal surgery had presented difficulties both with

maintaining the airway and with intubation. It was decided, therefore, to ventilate her lungs using TTJV before securing the airway with a tracheal tube.

The patient was premedicated with oral trimethoprim 3 mg kg⁻¹ and atropine 0.02 mg kg⁻¹ i.m., supplemented in the anaesthetic room with i.v. midazolam. Lignocaine with adrenaline was infiltrated into the pretracheal skin below the level of the cricoid cartilage. A 14-gauge VBM cricothyroid cannula (VBM Medizintechnik, W. Germany) was inserted into the trachea and connected to a Sanders oxygen injector. This type of cannula is manufactured from Teflon and is kink resistant. It has a Luer Lok connection for jet ventilation in addition to a 15-mm connection for use in an emergency with a respiratory bag or conventional ventilator. Its use has been advocated for paediatric ventilation for laser surgery and endoscopic procedures and in small children with laryngeal obstruction [1].

TTJV was performed using 50% oxygen in nitrous oxide.

This patient presented a grade IV difficult intubation according to the classification proposed by Cormack and Lehane [2]. Unsuccessful attempts to see the vocal cords were made with a variety of laryngoscopes, the larynx being viewed finally via an endview fiberoptic endoscope. This was inserted through the cords with 4.5-mm Portex tracheal tube fitting snugly over it. When visual confirmation of entry into the trachea was made, the Portex tube was passed through the

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larynx. TTJV continued without problem throughout this procedure until the tracheal tube was inserted through the larynx. Immediately following this manoeuvre, subcutaneous emphysema appeared at the root of the neck. Jet ventilation was stopped and the endoscope removed. Thereafter, the patient's lungs were ventilated with intermittent positive pressure via the oral tracheal tube. Clinical examination revealed signs of bilateral pneumothoraces, and two chest drains were inserted. The planned surgery was postponed and tracheotomy performed. The patient was transferred to the paediatric intensive care unit where the pneumothoraces resolved over the ensuing 4 days, with no evidence of persistent air leak.

Patient 2

A 60-yr-old man weighing 76 kg presented for laser surgery to a laryngeal tumour. He had noticed a change in his voice over several months, but did not complain of breathing difficulties. Clinical examination revealed a mild inspiratory stridor, poor dentition and an anticipated grade III difficult intubation [2]. Fibreoptic laryngoscopy under local anaesthesia had shown a supraglottic tumour obscuring 67% of the laryngeal inlet. Tomographic views of the neck revealed that the trachea was narrowed and deviated to the right. Palliative laser vaporization of the bulk of the tumour was planned in order to improve the patency of the airway.

Because of expected difficulty with intubation and requirements for good surgical access, trans-tracheal high frequency jet ventilation was chosen as the method of ventilation, with early recourse to tracheotomy if required.

Temazepam 30 mg was given orally as pre-medication. In the operating theatre an i.v. infusion was inserted i.v. and monitoring with pulse oximetry, ECG and non-invasive arterial pressure commenced. Oxygen was administered by mask and anaesthesia induced slowly with an i.v. infusion of propofol. A good airway was maintained easily and a cricothyroid puncture performed with a 12-gauge Wallace cannula. Neuromuscular block was produced with suxamethonium 100 mg i.v. Transtracheal high frequency jet ventilation (HFJV) was provided by the Penlon Bromsgrove Jet Ventilator set to deliver 120 b.p.m. at a driving pressure of 20 lbf in⁻² (138 kPa). Ventilation was monitored by observation of chest expansion and expiratory

gas flow through the mouth. Anaesthesia was maintained with an infusion of propofol and bolus doses of alfentanil and atracurium.

Laser surgery proceeded without difficulty for 1 h. At that time, however, tumour debris and bleeding became excessive and subcutaneous emphysema appeared at the root of the neck. The procedure was abandoned therefore, and a gum elastic bougie passed into the larynx. Trans-tracheal ventilation was stopped temporarily whilst a tracheal tube was passed, with difficulty, over the bougie. As the bougie was removed, a large escape of gas was heard at the proximal end of the tube. Manual ventilation of the lungs with 100% oxygen was commenced and tracheotomy performed. The patient's peripheral perfusion was poor and the pulse oximeter failed to register. Arterial pressure and ECG were unchanged. Auscultation suggested a right pneumothorax and a chest drain was inserted. A chest x-ray showed a left pneumothorax which was drained also and the patient's condition improved rapidly. Further radiographs demonstrated mediastinal emphysema, extensive subcutaneous emphysema and pneumoperitoneum. The neuromuscular block was antagonized and the patient allowed to wake up, following which he was transferred to the intensive therapy unit (ITU). The chest drains were clamped 24 h after admission to the ITU and removed within 48 h of insertion. Serial chest x-rays confirmed rapid resolution of both the pneumothoraces and emphysema, thus supporting the absence of a persistent air leak.

DISCUSSION

Various methods of jet ventilation or insufflation and air entertainment have been reported. Trans-tracheal jet ventilation was described in 1971 [3]. It has been advocated in situations where immediate tracheal intubation may not be possible [4] and in anaesthesia for direct laryngoscopy [5]. Tobias, Nassar and Richards reported a method of nasotracheal jet ventilation for microlaryngeal procedures using a Sanders injector [6]. The following year, Pybus, O'Connor and Henville devised a catheter technique using the control module of the Nuffield Anaesthetic Ventilator [7]. High frequency percutaneous transtracheal jet ventilation using a small catheter has also been studied [8]. The results showed adequate gas exchange at rates of ventilation up to 200 b.p.m. at tidal volumes approaching deadspace volume.

It has been advocated for use in both children [1] and adults [9] undergoing laser surgery of the larynx. Advantages of jet ventilation include a clear operative field for the surgeon [10], good respiratory gas exchange [11], elimination of the risk of ignition of a tracheal tube by laser [12] and decreased risk of broncho-aspiration of blood and debris [13].

Both of our patients suffered barotrauma following obstruction to expiration. Vivori [14] reported the death of a 4-yr-old child after excessive intrapulmonary pressure resulted in a massive right pneumothorax and cardiovascular collapse during use of a method of nasotracheal ventilation similar to that described by Pybus, O'Connor and Henville [7]. Rupture of the human lung is known to result also in interstitial emphysema and perivascular spread to the mediastinum [15].

The mechanism of barotrauma is open to speculation. It is probable that, in both patients, obstruction of the expiratory pathway during TTJV caused a sudden large increase in airway pressure and thus alveolar pressure, resulting in alveolar rupture, pulmonary interstitial emphysema, pneumomediastinum and pneumothorax. Indeed, in the second patient the pressure generated must have been so great as to force gas from the mediastinum into the peritoneal space. It is clear from both case reports that the initiation of barotrauma was a sudden, instantaneous event, as the patients did not suffer persistent pleural air leak.

Measurement of airway pressure is difficult using methods of jet ventilation and air entrainment. No attempts were made to measure airway pressure in these patients. Instead, as is common practice, reliance was placed upon close observation and a high index of suspicion to detect expiratory outflow obstruction. In patient No. 2 it is possible that the series of events may have been prevented by the monitoring of airway pressure.

The Penlon Bromsgrove Ventilator incorporates an airway monitoring system which can display baseline, mean or peak airway pressures. The mean airway pressure monitor has an upper alarm limit (overpressure) adjustable between 10 and 70 cm H₂O which, if activated, interrupts the driving gas. This facility has been utilized when performing HFJV via two insufflation catheters passed perorally into the trachea during laryngeal surgery. One catheter is used to deliver jet ventilation and the other to monitor airway

pressure. A modification of this concept in patient No. 2 by insertion of a second transtracheal cannula would have allowed increasing airway pressure to be detected and HFJV to be stopped automatically. A 22-gauge cannula would suffice for pressure monitoring purposes but, if venting of gas is required, a cannula of much larger diameter would be needed.

In patient No. 1, obstruction to expiration occurred when the fiberoptic endoscope and tracheal tube was inserted through the larynx. The patient has since undergone uneventful reconstructive surgery using an identical method of anaesthesia, with the exception that transtracheal jet ventilation was discontinued before instrumentation of the larynx. This ensured that no ventilation occurred whilst expiration was obstructed. In patient No. 2, expiratory obstruction occurred when blood and tumour debris suddenly became excessive.

This report emphasizes the need to ensure unobstructed expiration during transtracheal jet ventilation. It highlights the speed with which expiratory outflow obstruction can lead to severe and possible fatal barotrauma. We therefore advocate the use of a second percutaneous tracheal cannula for airway pressure monitoring during transtracheal HFJV.

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CORRESPONDENCE

BREATHING PATTERN AND PROPOFOL

Sir,—I was interested to read the recent paper by Goodman, Vanner and Wade [1] on the breathing pattern of anaesthetized patients in response to alfentanil and propofol. The authors' interpretation of the different effects of the two drugs is limited, in that it follows strictly the Oxford school on the study of breathing patterns and breath-time relationships. While most respiratory physiologists recognize the descriptive value of this approach to the study of ventilatory control, most would also regard it as singularly ineffective in revealing the neurophysiology of the respiratory controller.

Terms such as "on switches" have little meaning for the clinical anaesthetist, while carrying overtones similar to the "ego" of Freudian jargon—that is, there is no demonstrable "hardware" correlate. Recent evidence which suggests that propofol has a powerful depressant effect upon the peripheral chemoreceptors [2,3] has been omitted from the discussion. With this suggestion in mind, could the breathing pattern induced by propofol be interpreted differently?

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USE OF ALFENTANIL IN A PATIENT RECEIVING MONOAMINE OXIDASE INHIBITOR THERAPY

Sir,—There have been no previous reports on the use of alfentanil in patients taking monoamine oxidase inhibitors and undergoing anaesthesia [1]. I should like to report a case in which alfentanil was used in a patient receiving monoamine oxidase inhibitor (MAOI) therapy.

The patient was a 54-yr-old, 84-kg, hypertensive lady with chronic depression who had been treated with tranylcypromine for more than 15 yr. She presented with a history of several episodes of haemoptysis within the past 8 months and was scheduled for rigid bronchoscopic examination. She was otherwise asymptomatic. Her hypertensive disease was controlled with methyldopa 250 mg twice daily and she took tranylcypromine 10 mg and trifluoperazine 1 mg twice a day for depression. She had received a previous general anaesthetic (in 1973) before which her MAOI was stopped, and she could remember having a severe exacerbation of her depressive illness at that time.

Premedication was provided by temazepam 10 mg orally. Anaesthesia was induced with propofol 140 mg and maintained with an infusion of propofol 10 mg kg⁻¹ h⁻¹. She was given supplementary alfentanil in increments of 250 µg to a total of 2.5 mg. Neuromuscular block was facilitated with atracurium and the lungs were ventilated with 100% oxygen via a Sanders injector. Before induction, arterial pressure was 165/105 mm Hg and it settled at 120-150/85-100 mm Hg throughout the procedure, which lasted 30 min.

When the investigation was complete, the neuromuscular block was antagonized with neostigmine and atropine. The patient started to breathe spontaneously and woke up after 2-3 min. She was transferred to the recovery room where she remained awake and alert with an arterial pressure of 140/90 mm Hg, heart rate 75 beat min⁻¹ and ventilatory frequency 16-20 b.p.m.

Patients receiving MAOI therapy are a cause for concern to the anaesthetist because of the potential for serious drug interactions between these agents and opioid analgesics [1]. Although fatal reactions have been reported only in connection with the use of pethidine and related compounds, hypotension and loss of consciousness have occurred with morphine and there are only a few anecdotal reports to support the safety of fentanyl. There have been no previous reports on the use of alfentanil in these patients.

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EXTRADURAL OPIOIDS IN LABOUR

Sir,—We read with interest the editorial by Dr Felicity Reynolds on the subject of use of extradural opioids in labour [1]. This editorial coincided with her review of the maternal and fetal advantages of extradural analgesia for labour in the *British Medical Journal* [2]. Dr Reynolds' internationally recognized expertise, coupled with her important contributions to the evolution of obstetric extradural analgesia, make her a logical choice to voice our cause to the medical community at large.

Dr Reynolds has been an active investigator in the use of extradural opioids since their introduction to the obstetric setting, and recently she described the efficacy of fentanyl in relieving perineal pain when combined with bupivacaine [3]. However, when she states in her editorial: "...hypotension and instrumental deliveries are not avoided..." and "...it is questionable if the gain in enhanced analgesia outweighs the inconvenience of using a controlled drug..." [1] we believe, with respect, that her conclusions may be premature.

The majority of studies on fentanyl and sufentanil in obstetrics have used bolus injections of relatively concentrated bupivacaine. We agree that using opioids with an effective dose

of local anaesthetic holds little advantage, and in fact adds the possibility of additional side effects to those possessed by bupivacaine. If the therapeutic goal is to reduce the chance of bupivacaine toxicity and eliminate motor paralysis without compromising the quality of analgesia, then bolus dosing of high concentrations of bupivacaine with either fentanyl or sufentanil at the beginning of labour may not be the method of choice.

In contrast, investigation of the efficacy of bupivacaine combined with either fentanyl or sufentanil given by continuous extradural infusion in parturients has been infrequent, particularly from Europe. There may be factors unknown to us that have influenced the paucity of opioid infusion studies from Europe. Two recent reports from Chestnut and colleagues [4,5] suggest that this technique with low dose bupivacaine (0.0625%) and fentanyl (0.0002%) may be promising. They found good to excellent analgesia in 96–98% of their parturients during the first stage of labour; motor block was present in only 5% of mothers whilst using a bupivacaine concentration virtually devoid of the risk of toxicity [4]. The absence of motor paralysis is probably the most distinct advantage of the use of local anaesthetic-opioid combinations, even if analgesic quality is not improved. In addition, in their most recent study Chestnut and colleagues have shown that a 0.0625% bupivacaine–0.0002% fentanyl mixture carried through the second stage provided good to excellent analgesia in 76% of mothers *without* increasing the rate of instrumental delivery or Caesarean section [5].

Our recent clinical experience with both bupivacaine–fentanyl and bupivacaine–sufentanil at these low dose infusion concentrations have proven equally encouraging. Consequently, we are launching a two-centre double-blind, randomized study to compare these local anaesthetic-opioid combinations with bupivacaine alone for: efficacy in relieving pain, speed of onset and quality of analgesia, extent of motor block, duration of the first and second stages of labour and incidence of instrumental delivery. We hope to show that a combined opioid–local anaesthetic extradural infusion technique possesses advantages.

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Sir,—I thank Dr Herman and his colleagues for their kind remarks, and concur that extradural infusions of local anaesthetic-opioid combinations are the way ahead.

I am aware of the excellent U.S. research on this subject and, indeed, made reference to it in my editorial, but I acknowledge that I gave it less weight than I would now. I have since been educated further by the North American Experience. It appears that opioids make extradural infusions a feasible proposition, and infusions do the same for opioids—in that the combination greatly reduces the need for top-up doses.

Moreover, it would appear from the evidence of Naulty, Ross and Bergen [1] that the combination of a small dose of sufentanil (5 µg) with only 0.0312% bupivacaine provides a real advantage of good analgesia and complete absence of motor block—suggesting genuine evidence of potentiation of analgesia, rather than a simple additive effect that has been demonstrated with other combinations. This information was not available to me when I wrote my editorial in February 1989.

I think I can suggest why we have been laggard in conducting opioid infusion studies in the U.K. First, we have *not* been plagued by the spectre of bupivacaine toxicity as have those in North America, and we have had no maternal deaths reported from this cause. It would appear from this that accidental i.v. injection is less of a problem in the U.K., for three possible reasons: we use a catheter without a guide wire, which may be less likely to penetrate a blood vessel; many of us use three-holed catheters, which reduces the likelihood of a false negative aspiration test; and the use of an extradural filter slows the rate of injection. The second reason that few of us have hitherto reported using opioid infusions is that we have midwives to undertake top-up injections and therefore the need to reduce the frequency of top-ups is less. The third reason is probably a paucity of infusion pumps coupled, perhaps erroneously, with a desire not to “hitch up” women to yet another gadget. We may be proven incorrect.

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BOOK REVIEWS

Anesthesia and the Heart Patient. Edited by F. G. Estafanous. Published by Butterworths, Boston, London, Singapore, Sydney, Toronto, Wellington. Pp. 367; indexed; illustrated. Price £50.

This book evolved from a symposium held in 1986 sponsored by the Cleveland Clinic Foundation on "Anesthesia and the Heart Patient". It does not set out to be a general text book of cardiovascular anaesthesia, but the editor's hope is that it would be a forum for the presentation and exchange of the latest knowledge on clinical experience and patient management from distinguished experts from around the world.

Unfortunately, it appears to have sacrificed the comprehensive coverage expected from a conventional text book, without fulfilling the promise of presenting the developing frontiers of the specialty. As is probably inevitable in any book in which experts in a field are asked to review anaesthesia for a particular procedure, there is considerable repetition which could have been edited out by combining some aspects of patient management into more broadly based chapters. Some of the chapters are too short to have any real value; for example, a chapter on myocardial protection which consists of three pages and has only six references, would appear to have little value and could have been omitted, although the topic itself is of vital and central importance to the management of patients during open heart surgery. The chapter on cardiopulmonary bypass is slightly longer, with four pages of text, but again seems to add nothing of merit to knowledge on the subject; surprisingly for a symposium held in 1986, no mention is made of the relative merits of pH or alphasat in management of acid-base balance during cardiopulmonary bypass. In addition, in this chapter a most remarkable concept is advanced, with the suggestion that the reference pressure for the circulation during cardiopulmonary bypass should be related to the lowest negative pressure generated in the venous drainage to the oxygenator. It is suggested that computations such as systemic vascular resistance and effective perfusion pressure should be calculated with reference from the arterial pressure to the lowest negative pressure generated in the extracorporeal circuit. The perfusion pressure "seen" by organs is from that developed in the arterial tree to that existing in the venous system in the patient, which is normally near atmospheric pressure, but is certainly much greater than that generated at the lowest point of the venous drainage pipes when they reach the oxygenator.

It is also remarkable, in an admittedly very short section on pulsatile flow, to see no reference to the work of Taylor and colleagues on the hormonal and metabolic changes related to the use of pulsatile and non-pulsatile flow.

Some chapters are worth reading; in particular those relating to coronary artery surgery, where the epidemiology and long term results are well reviewed; and the chapter on the future of mechanical assist devices in the artificial heart presents a good review on the subject and an excellent list of references for further reading.

The chapter entitled "Heterogeneity of Monitored Parameters" is interesting and presents some of the bizarre

changes which occur both in the electrical performance of the myocardium and in haemodynamic monitoring of patients immediately before and after cardiopulmonary bypass. This chapter is well referenced and would form a good guide to those looking for information on monitoring during cardiac surgery.

The chapters on anaesthetic agents and vasoactive drug pharmacology are very weak and present no new information for any practising clinician. Inotropic agents, in particular, rate less than three pages of text, and it is difficult to see any information in that chapter which is not well known to any clinical anaesthetist.

It is difficult to suggest to whom this book could be recommended. There is no way in which it would be used in place of a standard textbook on cardiac anaesthesia. However, if a departmental library wishes to have a comprehensive selection of all the books available on anaesthesia and the heart patient, it may be desirable to include this one on the shelves. Apart from one or two chapters, it does not present any new information which will be useful to clinicians practising in the field of cardiovascular anaesthesia.

D. W. Bethune

Cardiac Arrhythmias, 3rd Edn. By D. H. Bennett. Published (1989) by Butterworth & Co., Guildford. Pp. 206; indexed; illustrated. Price £16.50.

Cardiac arrhythmias are common in surgical patients presenting for procedures under local or general anaesthesia. Recognition of the type of arrhythmia is often not easy and access to a clear, concise and well written monograph is a considerable help. In this third edition of a book first published in 1987, Dr Bennett's aim is "to provide a practical guide to the diagnosis, investigation and management of the main cardiac arrhythmias...". Deliberately, the style is direct, the illustrations abundant and there is no attempt at devising complex diagrams to explain what can be described very adequately in plain words. This, combined with the numerous and well chosen tracings, makes the book very easy to read.

In addition to a description of all the common (and some not so common) arrhythmias, therapy is discussed in terms of anti-arrhythmic drugs, cardioversion, temporary and long-term cardiac pacing. There are also short sections on ambulatory ECG monitoring and intracardiac electrophysiological testing. A very useful summary of the main points completes each chapter. Finally, those whose have read the book from cover to cover will enjoy the quiz: arrhythmias for interpretation.

This book has not been written for anaesthetists and, therefore, one should not expect to find answers to all the specific questions we have to ask ourselves. However, it is of such clarity and it is so practical that the frustration of wondering about arrhythmias should essentially disappear after reading it.

P. Foëx

Malignant Hyperthermia: Current Concepts. Edited by M. Felipe, S. Gottmann and H. J. Khambatta. Published by Normed Verlag, Homburg. Pp. 220; indexed; illustrated. Price DM 49.00.

In the brief preface to their book, Professor Felipe suggests that "fatality from MH remains very high in many countries" because "there are no centers...to test for patients' susceptibility to MH." Could this be a *cri du coeur*, as the International Course on MH held in Barcelona in 1988 provides the textual basis of this book, and Spain remains one of the few European countries not to have representation in the European MH Group? However, MH is clearly widely recognized in Spain and the book contains case report contributions by 19 Spanish anaesthetists.

The list of contributors suggests that this International Course was conceived with care and selectivity such that, of the 40 contributors, 20 are from Spain, four each from Lille, Philadelphia and Taiwan, and five from West Germany. Considering this was an International meeting held in Europe, it is surprising the organizers have not included more contributions from members of the European MH Group. Notable contributions were made by Dr Britt from Toronto and Professor Rosenberg from Philadelphia, who between them have written seven of the 14 chapters.

I found this a difficult book to read, although it does contain a lot of useful information. Perhaps in the interests of international diplomacy, there is less than optimal editorial censorship: the editors have retained three identical structural formulae of dantrolene sodium and have printed some trivial cartoons which add nothing. Overall, the standard of the illustrations is poor, with fading muscle twitch traces and some graphs with undecipherable axes. Each illustration is idiosyncratic and this may underline the problems in trying to use book illustrations which have been taken directly from 35-mm slides.

After a lengthy panel discussion which seems to have been reproduced *verbatim*, including colloquialisms, there are a series of appendices containing two wall chart summaries of treatment of the MH crisis, one describing the summary treatment of NMS and acute febrile catatonia (are they the same?) and the chemical and pharmacological characteristics of dantrolene. The book ends with a useful list of "Hot lines and laboratories" worldwide where patients may be investigated.

I cannot recommend this book for the anaesthetist in training, because there are many unsubstantiated statements which could significantly influence clinical practice detrimentally. However, a sophisticated reader might benefit from a careful perusal of selected topics.

F. R. Ellis

The History of Anaesthesia. (International Congress and Symposium Series No. 134.) Edited by R. S. Atkinson and T. B. Boulton. Published (paperback) by Royal Society of Medicine Services Ltd, London. Pp. 630; indexed; illustrated. Price £40.00.

This volume contains the proceedings of the Second International Symposium on the History of Anaesthesia held in London on July 20-23, 1987. It is made up of seven parts, comprising 27 chapters.

The first part consists of special presentations and includes a number by British pioneers, including the late Sir Robert

MacIntosh, the late J. Alfred Lee, Professor W. W. Mushin, C. F. Scurr and Professor T. Cecil Grey.

The second part consists of the early development of organizations in anaesthesia and includes chapters on the origins of anaesthesia, the introduction of anaesthesia in the U.S.A., the spread of the news to the United Kingdom and throughout Europe and further, and the organizations for the specialty of anaesthesia, Military anaesthesia and the transport of casualties.

The third part is based on the history of anaesthetic agents, with chapters on all inhalation agents, chloroform, neuromuscular blocking agents and miscellaneous agents. The fourth part describes the history of anaesthetic apparatus, including anaesthetic machines, breathing machines and inhalers. The fifth is concerned with the history of resuscitation and intensive care, with chapters on resuscitation through the ages, early attempts at expired air resuscitation, intubation and manual ventilation, artificial ventilation, transfusion, pulmonary and cardiac surgery and resuscitation.

The sixth part consists of biographies with chapters on developments before 1846 (the pathfinders), 1846-1880 (the pioneers) and after 1880 (the developers). Part seven consists of special presentations related to posters and video film presentations as a list.

In common with many Proceedings, this book has a number of papers which are duplicative and, although a theme is organized through each part and chapter, there are a few areas in which there are disjointed papers.

The book covers many aspects of the history of anaesthesia and is of special interest to historians in this specialty. Several papers are referenced and illustrated, thus providing an invaluable addition to the library of anaesthetists and anaesthetic historians.

I. McLellan

Safety and Cost Containment in Anaesthesia. Edited by J. S. Gravenstein and J. F. Holzer. Published by Butterworths, Guildford. Pp. 257; indexed; illustrated. Price £22.95.

Throughout the past 150 years anaesthesia morbidity and mortality rates have declined, despite growing surgical sophistication, more operations being performed, especially at the extreme ages of life, and more patients presenting as critically ill. Indeed, anaesthetists have repeatedly evaluated the nature of risks in anaesthesia and have made efforts to reduce them. The specialty is considered by many to be the leader in medical risk management and patient safety. This position has been attained by attention to several factors which include: the early measurement of risks, the provision of postgraduate courses and meetings, the institution and inspection of comprehensive training programmes, and the development of new technology.

This is a superb book which could not have arrived at a better time, especially as the medical profession in the U.K. is now grappling with the spectre of resource management, proposed changes in practice and funding of the service, the introduction of audit and peer review, and the handicap of massive medico-legal premiums and malpractice settlement costs. It is one of the most important books to be published in the specialty of anaesthesia for some years. The subject is, of course, safety and the costs of anaesthesia care, and how the two relate. There are 25 eminent contributing authors ranging from senior anaesthetists to experts on purchasing, risk management, lawyers, major equipment manufacturers and

suppliers, and experts from various other walks of life. There is virtually no overlap or inconsistency and, although it is true that all the contributors hail from the U.S.A., this in fact does not present any problems, as adequate considerations of European studies are included. Each contributor has provided a thoughtful, readable and comprehensive input which makes very good sense. The book is well referenced throughout and contains both an author and a subject index.

This book represents excellent value for money and is essential reading for all anaesthetists, and health care professionals involved with the specialty. Nowhere else are all the relevant topics gathered together so comprehensively and yet so succinctly; there is a tremendous amount of information in this book, which also gives plenty of food for thought about the future of our specialty.

Anthony P. Adams

Essentials of Critical Care Medicine. By M. J. Tobin. Published by Churchill Livingstone Publishers, New York, Edinburgh, London, Melbourne. Pp. 300; illustrated. Price £19.95.

Essentials of Critical Care Medicine is a single-author handbook comprising 18 chapters. The reader is informed in the Foreword that the author, Martin J. Tobin, Associate Professor of Internal Medicine, the University of Texas Health Science Centre, Houston, has broad training and expertise in Internal Medicine, including the sub-specialties of respiratory and critical care medicine.

The handbook is intended specifically for medical students and internal medicine residents in the course of their I.C.U. rotation, or those preparing for certification examinations in critical care medicine. The Foreword emphatically states that the manual is not intended for surgeons or anaesthetists managing postoperative and trauma victims.

The two chapters devoted to cardiovascular and respiratory disorders constitute over 50% of the text. The remainder of the text includes chapters on renal and acid-base disorders, nutrition, infectious diseases, gastrointestinal, haematological and neurological disorders. To satisfy the requirements of the American Board of Internal Medicine, chapters featuring the medical management of trauma and burns, perioperative problems and obstetric critical care are included reluctantly.

This critical care manual has a number of pleasant and commendable features. The single-author text avoids much of the overlap, repetition, and conflicting opinions so characteristic of multi-author texts. The information contained in many chapters, especially infectious diseases, renal and gastrointestinal disorders, is succinct and precise. Fellowship and Board certification examination candidates will appreciate the liberal use of tables and figures and the common sense approach and priorities ascribed to management of common clinical critical care situations. Each section is followed by a list of suggested reading material related directly to the topic discussed. Most of the articles and texts suggested by the author are current and appropriate. The manual layout is imaginative and no effort has been spared to make the reader's task less onerous.

This manual, however, has a number of deficiencies for the practising anaesthetist with a passing interest in critical care medicine. This reviewer's main criticism relates to the selection of topics and the priority assigned. Shock, acute

respiratory failure, principles of mechanical ventilation and several important other topics could have received a more extensive emphasis from the author. The presentation of topics in the crucial respiratory and cardiovascular chapters does not follow any logical progression: physiology, anatomy, clinical disease entities, invasive-non invasive assessment, monitoring, treatment, etc. The topics in these two chapters bear no relationship to one another and each section stands as a separate and independent entity. The author must, of necessity, take a significant body of information from better known and established sources. For example the section on cardiopulmonary resuscitation is taken almost directly from the American Heart Association standards and guidelines.

Despite the above limitations, this text should still be a worthwhile purchase by Final Fellowship candidates. Better critical care reference text books are available for Department of Anaesthesia/Critical Care/I.C.U. Libraries.

The author must be commended on the onerous task of single-handedly compiling this handbook. The work must have been time consuming and exhausting. Dr Tobin must be a very well informed physician; to paraphrase Oliver Goldsmith... "and still they gazed, and still the wonder grew, that one small head could carry all he knew."

Anthony J. Cunningham

Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in Anaesthesiology, Volume 15. Edited by J. B. Lofstrom and U. Sjostrand. Published by Elsevier, Amsterdam, New York, Oxford. Pp. 325; indexed; illustrated. Price US \$144.75, Dfl. 275.00.

The editors of the series, *Monographs in Anaesthesiology*, have done well to select a Swedish team for the editorship of a volume on local anaesthesia. This is a fascinating book. It is the perfect complement to all the various how-to-do-it texts that have been published recently. The chapters cover a selection of well-chosen subjects that form a vital, up to date, academic background to the practice of local anaesthesia. I must admit to a personal bias, as this is the aspect of local anaesthesia I myself find most interesting.

The authorship, principally Scandinavian, comprises names that are pre-eminent in the field. Each has written a scholarly and well referenced review of his subject which appears in immaculate English. Most authors have avoided the amateurish use of the first person when reporting their own work. Chapters include chemistry, distribution, systemic effects, nerve toxicity (?), anatomy, sensory, sympathetic and motor block, effects of regional block on placental blood flow, antithrombotic, immunological, psychological and stress related effects, spinal opioids and, rather unexpectedly and down to earth, local anaesthesia in difficult environments.

There is some minor overlap, for example tables of pK_a and partition coefficients (acceptably consistent) appear twice, as do descriptions of newer agents—only one overlap here, ropivacaine; incidentally, synthesis as a racemate was reported first in 1957 by the Bofors team (af Ekenstam and colleagues, *Acta Chemica Scandinavica* 1957; 11: 1183), although this is not generally acknowledged, as Astra, who bought up Bofors, market ropivacaine as the L-isomer.

The spelling is British, although the drug names such as lidocaine and tetracaine, are USP. The old fashioned spelling "foetus" is still used. There is a comprehensive index for the

whole book, which was prepared probably by the publishers, as "opiates" and "opioids", used indiscriminately in the text, have been indexed separately. Epidural is indexed as extradural, although happily in the text the more speaker-friendly term is used (*pace* the editorship of this journal!).

However, any criticisms I might make are minor. This book is worth buying for any anaesthetic library, and will be invaluable for those writing exams or wishing to research the subject of local anaesthesia.

F. Reynolds

Advances in Pain Research and Therapy, Vol. II, 1st Edn.

Edited by C. Stratton Hill jr and W. S. Fields. Published by Raven Press, New York. Pp. 380; indexed; illustrated. Price US \$107.50.

This book is the Proceedings of a meeting held in Houston in March, 1988. The stimulus for the meeting was the difficulties which society has in sanctioning the medical use of opioids, because of their possible misuse. The political perception is that medical availability of opioids is a factor in creating a "street problem" and that patients prescribed opioids may become addicts. From the clinical perspective, the ability to prescribe opioids to patients who will benefit may be restricted by such perceptions; indeed, this is the case in many countries

of the world. Oral opioids are unavailable for cancer pain management in 30% of the world.

The speakers at the conference came from a variety of backgrounds: cancer pain management, analgesic studies, pharmacology, philosophy, history and, indeed, government legislators. Although a great deal of the information in individual chapters is available in other places, the book does draw together useful and eclectic literature because of the variety in backgrounds of the authors.

Any anaesthetist who is having problems achieving support for effective postoperative pain relief should use Dr Jaffe's chapter as ammunition. He gives three vignettes, from three decades, and each shows the human misery caused by inadequate prescription. The inadequacy was caused by the prescriber's ignorance.

This book is written from an American perspective, but the moral of the story is the same everywhere. Patients may be deprived of beneficial treatment with opioids because of ill founded fears of the prescriber, the person giving the drug, the pharmacist making up the prescription and, indeed, the patients themselves. There is more than enough information in this book to deal with these fears.

Although current controversy in this country centres more on the use of opioids in non-malignant pain, this book is a useful source for those who think it important that we should be free to prescribe opioids if they are an effective remedy and there is no alternative.

H. McQuay

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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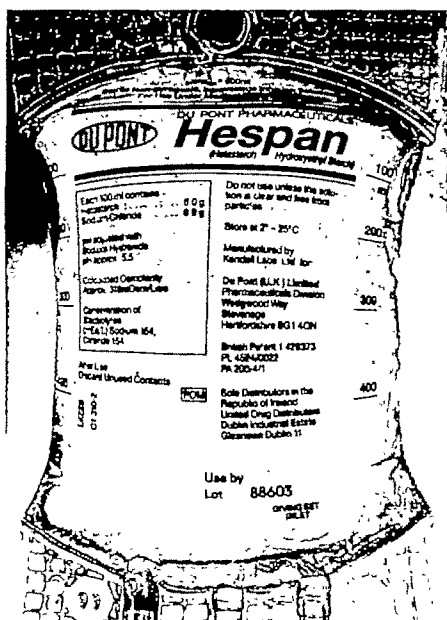
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